(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/10436 A2

(51) International Patent Classification[7]: C12Q 1/00

(21) International Application Number: PCT/US01/23642

(22) International Filing Date: 27 July 2001 (27.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/222,093 28 July 2000 (28.07.2000) US

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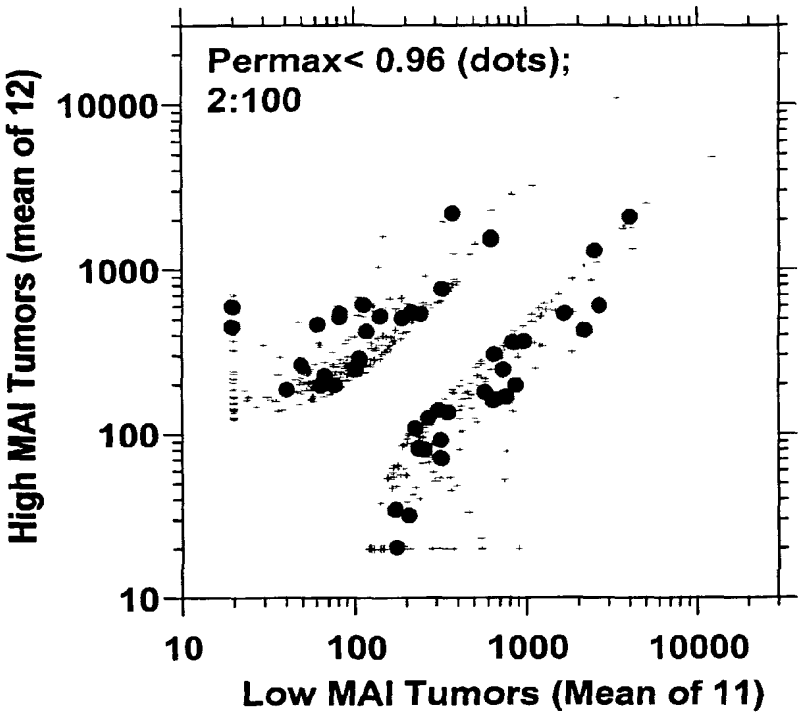
(81) Designated States *(national)*: CA, JP.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROGNOSTIC CLASSIFICATION OF BREAST CANCER



(57) Abstract: The invention provides particular sets of genes that are expressed differentially in tumors characterized as high MAI or low MAI tumors. These sets of genes can be used to discriminate between high and low MAI tumors. Diagnostic assays for classification of tumors, prediction of tumor outcome, selecting and monitoring treatment regimens and monitoring tumor progression/regression are also provided.

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PROGNOSTIC CLASSIFICATION OF BREAST CANCER

Field of the Invention

The invention relates to nucleic acid microarray markers for cancer, particularly for breast cancer. The invention also relates to methods for diagnosing cancer as well as optimizing cancer treatment strategies.

Background of the Invention

Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast (Harrison's Principles of Internal Medicine 1998). Although much progress has been made toward understanding the biological basis of cancer and in its diagnosis and treatment, it is still one of the leading causes of death in the United States. Inherent difficulties in the diagnosis and treatment of cancer include among other things, the existence of many different subgroups of cancer and the concomitant variation in appropriate treatment strategies to maximize the likelihood of positive patient outcome.

The traditional method of breast cancer diagnosis and staging is through the use of biopsy examination. Once a diagnosis is made, the options for treating breast cancer are assessed with respect to the needs of the patient. These options traditionally include surgical intervention, chemotherapy, radiotherapy, and adjuvant systemic therapies. Surgical therapy may be lumpectomy or more extensive mastectomy. Adjuvants may include but are not limited to chemotherapy, radiotherapy, and endocrine therapies such as castration; administration of LHRH agonists, antiestrogens, such as tamoxifen, high-dose progestogens; adrenalectomy; and/or aromatase inhibitors (Harrison's Principles of Internal Medicine 1998).

Of key importance in the treatment of breast cancer is the selection and implementation of an appropriate combination of therapeutic approaches. For example, depending on a breast cancer patient's prognosis, therapy may include surgical intervention in combination with adjuvant therapy or it may only include surgical intervention. In addition, for some patients pretreatment with chemotherapy or radiotherapy is utilized prior to surgical intervention, but in other patients adjuvant therapies are used following surgical intervention.

It is difficult to predict from standard clinical and pathologic features the clinical course of early stage breast cancer, particularly lymph node-negative tumors in

premenopausal patients. Current practice in the United States is to offer systemic chemotherapy to most of these women. Because the majority of these women would have good outcome even without chemotherapy, the rate of "over-treatment" is high. Chemotherapy itself carries a 1% mortality rate. Therefore, unnecessary deaths could be avoided if it were possible to subdivide these patients into high and low risk subgroups, and only undertake adjunctive treatment for those judged to be high risk.

Selection of a suitable treatment regimen for breast cancer is based on the subgroup of cancer. Current strategies used to make therapeutic decisions in the management of patients with breast cancer are based on several factors including hormone receptor status, her-2/neu staining, flow cytometry, and the mitotic activity index (MAI). The MAI is a widely utilized predictor of outcome in cancers, particularly in invasive breast cancer. The definition of the MAI is "the total number of mitoses counted in 10 consecutive high-power fields (objective, x40; numeric aperture, .75; field diameter, 450 microns), in the most cellular area at the periphery of the tumor, with the subjectively highest mitotic activity" (Jannink et al., 1995). For the procedure, hematoxylin-eosin stained sections of breast cancer tumor are assessed for the total number of mitotic figures in ten consecutive high-power fields and based on these numbers the breast cancer is assigned to either good outcome (MAI<10) or poor outcome (MAI>10). MAI classification correlates to standard parameters such as death, recurrence, and metastases, which are known to those of ordinary skill in the art to predict clinical outcome.

Determination of appropriate treatment for an individual cancer patient is complex with a wide variety of treatments and possible treatment combinations. For example, chemotherapy is a common method of cancer treatment, with more than 50 different chemotherapeutic agents available. These therapeutic agents can be used in a wide range of dosages both singly and in combinational therapies with other chemotherapeutic agents, surgery, and/or radiotherapy.

The available methods for designing strategies for treating breast cancer patients are complex, time consuming, and inexact. The wide range of cancer subgroups and variations in disease progression limit the predictive ability of the healthcare professional. In addition, continuing development of novel treatment strategies and therapeutics will result in the addition of more variables to the already complex decision-making process involving matching the cancer patient with a treatment regimen that is appropriate and optimized for the cancer stage, extent of infiltration, tumor growth rate, and other factors central to the

individual patient's prognosis. Because of the critical importance of selecting appropriate treatment regimens for breast cancer patients, the development of guidelines for treatment selection is of key interest to those in the medical community and their patients. Thus, there presently is a need for objective, reproducible, and sensitive methods for predicting breast cancer patient outcome and selecting optimal treatment regimens.

Summary of the Invention

It now has been discovered that particular sets of genes are expressed differentially in tumors characterized as high MAI or low MAI tumors. These sets of genes can be used to discriminate between high and low MAI tumors. Accordingly, diagnostic assays for classification of tumors, prediction of tumor outcome, selecting and monitoring treatment regimens and monitoring tumor progression/regression can now be based on the expression of sets of genes.

According to one aspect of the invention, methods for diagnosing breast cancer in a subject suspected of having breast cancer are provided. The methods include obtaining from the subject a breast tissue sample and determining the expression of a set of nucleic acid molecules or expression products thereof in the breast tissue sample. The set of nucleic acid molecules includes at least two nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51. In preferred embodiments, the breast tissue sample suspected of being cancerous.

In some embodiments the set of nucleic acid molecules includes more than 2 and up to all of the nucleic acid molecules set forth as SEQ ID NOs:1-51, and any number of nucleic acid sequences between these two numbers. For example, in certain embodiments the set includes at least 3, 4, 5, 10, 15, 20, 30, 40 or more nucleic acid molecules of the nucleic acid molecules set forth as SEQ ID NOs:1-51.

In other embodiments, the method further includes determining the expression of the set of nucleic acid molecules or expression products thereof in a non-cancerous breast tissue sample, and comparing the expression of the set of nucleic acid molecules or expression products thereof in the breast tissue sample suspected of being cancerous and the non-cancerous breast tissue sample.

According to another aspect of the invention, methods for identifying a set of nucleic acid markers or expression products thereof are provided. The methods are effective for determining the prognosis of cancer. The methods include obtaining a plurality of tumor

tissue samples from a plurality of subjects afflicted with cancer, classifying the plurality of tumor tissue samples according to mitotic activity index (MAI) into high MAI and low MAI groups and determining differences in the expression of a plurality of nucleic acid molecules or expression products thereof in the tumor tissue samples. The methods further include selecting as a set of nucleic acid markers the nucleic acid molecules or expression products thereof which are differentially expressed in the high MAI and the low MAI groups. The set of nucleic acid markers or expression products thereof effective for determining poor prognosis of cancer includes one or more nucleic acid molecules or expression products thereof which are preferentially expressed in high MAI tumor tissue samples, and wherein the set of nucleic acid markers or expression products thereof effective for determining good prognosis of cancer comprises one or more nucleic acid molecules or expression products thereof which are preferentially expressed in low MAI tumor tissue samples. In preferred embodiments, the cancer is breast cancer.

According to still another aspect of the invention, methods for selecting a course of treatment of a subject having or suspected of having cancer are provided. The methods include obtaining from the subject a tissue sample suspected of being cancerous, determining the expression of a set of nucleic acid markers or expression products thereof which are differentially expressed in high MAI tumor tissue samples to determine the MAI of the tissue sample of the subject, and selecting a course of treatment appropriate to the cancer of the subject.

In preferred embodiments the cancer is breast cancer, and in some of these embodiments the methods include determining the expression of a set of nucleic acid markers that are differentially expressed in low MAI breast tumor tissue samples.

According to yet another aspect of the invention, methods for evaluating treatment of cancer are provided. The methods include obtaining a first determination of the expression of a set of nucleic acid molecules or expression products thereof, which are differentially expressed in high MAI tumor tissue samples to determine the MAI of the tissue sample from a subject undergoing treatment for cancer, and obtaining a second determination of the expression of a set of nucleic acid molecules or expression products thereof, which are differentially expressed in high MAI tumor tissue samples to determine the MAI of the second tissue sample from the subject after obtaining the first determination. The methods also include comparing the first determination of expression to the second determination of expression as an indication of evaluation of the treatment.

In preferred embodiments the cancer is breast cancer, and in some of these embodiments the methods include determining the expression of a set of nucleic acid markers that are differentially expressed in low MAI breast tumor tissue samples.

The invention in another aspect provides solid-phase nucleic acid molecule arrays. The arrays have a cancer gene marker set that consists essentially of at least two and as many as all of the nucleic acid molecules set forth as SEQ ID NOs:1-51 fixed to a solid substrate. The set of nucleic acid markers can include any number of nucleic acid sequences between these two numbers, selected from SEQ ID NOs:1-51. For example, in certain embodiments the set includes at least 3, 4, 5, 10, 15, 20, 30, 40 or more nucleic acid molecules of the nucleic acid molecules set forth as SEQ ID NOs:1-51. In some embodiments, the solid-phase nucleic acid molecule array also includes at least one control nucleic acid molecule.

In certain embodiments, the solid substrate includes a material selected from the group consisting of glass, silica, aluminosilicates, borosilicates, metal oxides such as alumina and nickel oxide, various clays, nitrocellulose, or nylon. Preferably the substrate is glass.

In other embodiments, the nucleic acid molecules are fixed to the solid substrate by covalent bonding.

According to yet another aspect of the invention, protein microarrays are provided. The protein microarrays include antibodies or antigen-binding fragments thereof, that specifically bind at least two different polypeptides selected from the group consisting of SEQ ID NOs:52-102, fixed to a solid substrate. In some embodiments, the microarray comprises antibodies or antigen-binding fragments thereof, that bind specifically to least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 or 51 different polypeptides selected from the group consisting of SEQ ID NOs:52-102. In certain embodiments, the microarray also includes an antibody or antigen-binding fragment thereof, that binds specifically to a cancer-associated polypeptide other than those selected from the group consisting of SEQ ID NOs:52-102, preferably a breast cancer associated polypeptide. In some embodiments, the protein microarray also includes at least one control polypeptide molecule. In further embodiments, the antibodies are monoclonal or polyclonal antibodies. In other embodiments, the antibodies are chimeric, human, or humanized antibodies. In some embodiments, the antibodies are single chain antibodies. In still other embodiments, the antigen-binding fragments are $F(ab')_2$, Fab, Fd, or Fv fragments.

In a further aspect of the invention, methods for identifying lead compounds for a pharmacological agent useful in the treatment of breast cancer are provided. The methods include contacting a breast cancer cell or tissue with a candidate pharmacological agent, and determining the expression of a set of nucleic acid molecules in the breast cancer cell or tissue sample under conditions which, in the absence of the candidate pharmacological agent, permit a first amount of expression of the set of nucleic acid molecules. The set of nucleic acid molecules includes at least two and as many as all of the nucleic acid molecules set forth as SEQ ID NOs:1-51. The methods also include detecting a test amount of the expression of the set of nucleic acid molecules, wherein a decrease in the test amount of expression in the presence of the candidate pharmacological agent relative to the first amount of expression indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which is useful in the treatment of breast cancer. In preferred embodiments, the set of nucleic acid molecules is differentially expressed in high MAI breast tumor tissue samples.

In some embodiments of any of the foregoing methods and products, the differences in the expression of a the nucleic acid molecules are determined by nucleic acid hybridization or nucleic acid amplification methods. Preferably the nucleic acid hybridization is performed using a solid-phase nucleic acid molecule array. In other embodiments, the differences in the expression of the nucleic acid molecules are determined by protein expression analysis, preferably SELDI mass spectroscopy.

These and other aspects of the invention will be described in greater detail below.

Brief Description of the Drawings

Figure 1 is a scatterplot of gene expression level in low risk (x axis) and high risk (y axis) breast cancers. 422 genes whose mean expression between groups differs at least 2-fold and by 100 expression units are shown as small crosses. The top 51 t-test ranked genes with Permax 0.96 are indicated as solid circles, and appear in Table 1.

Detailed Description of the Invention

The invention described herein relates to the identification of a set of genes expressed in breast cancer tissue that are predictive of the clinical outcome of the cancer. Changes in cell phenotype in cancer are often the result of one or more changes in the genome expression of the cell. Some genes are expressed in tumor cells, and not in normal cells. In addition, different genes are expressed in different subgroups of breast cancers, which have different

prognoses and require different treatment regimens to optimize patient outcome. The differential expression of breast cancer genes can be examined by the assessment of nucleic acid or protein expression in the breast cancer tissue.

The genes were identified by screening nucleic acid molecules isolated from various breast cancer samples for expression of the genes present on a high-density nucleic acid microarray. The breast cancer samples were categorized with respect to their mitotic activity index (MAI) and the MAI was correlated to gene expression to identify those genes differentially expressed between low and high-MAI breast cancer tissue. The MAI has been shown to correlate with the outcome of the cancer as defined by tumor metastasis, tumor recurrence or mortality. Accordingly the genes identified permit, *inter alia*, rapid screening of cancer samples by nucleic acid microarray hybridization or protein expression technology to determine the expression of the specific genes and thereby to predict the outcome of the cancer. Such screening is beneficial, for example, in selecting the course of treatment to provide to the cancer patient, and to monitor the efficacy of a treatment.

The invention differs from traditional breast cancer diagnostic and classification techniques including MAI, hormone receptor expression and her-2/neu expression, with respect to the speed, simplicity, and reproducibility of the cancer diagnostic assay. The invention also presents targets for drug development because it identifies genes that are differentially expressed in poor outcome breast tumors, which can be utilized in the development of drugs to treat such tumors, e.g., by reducing expression of the genes or reducing activity of proteins encoded by the genes.

The invention moves beyond the use of the MAI and simplifies prognosis determination by providing an identified set of genes whose expression in breast cancers predicts poor clinical outcome as defined by tumor metastasis, recurrence, or death. In the invention, the MAI was used in conjunction with RNA expression phenotyping performed using high density microarrays generated from quantitative expression data on over 5000 (estimated 5800) genes, which have been analyzed to identify 51 specific probe sets (genes) with divergent expression between MAI groups. The expression gene set has multifold uses including, but not limited to, the following examples. The expression gene set may be used as a prognostic tool for breast cancer patients, to make possible more finely tuned diagnosis of breast cancer and allow healthcare professionals to tailor treatment to individual patients' needs. The invention can also assess the efficacy of breast cancer treatment by determining progression or regression of breast cancer in patients before, during, and after breast cancer

treatment. Another utility of the expression gene set is in the biotechnology and pharmaceutical industries' research on disease pathway discovery for therapeutic targeting. The invention can identify alterations in gene expression in breast cancer and can also be used to uncover and test candidate pharmaceutical agents to treat breast cancer.

Although the invention is described primarily with respect to breast cancer, one of ordinary skill in the art will appreciate that the invention also is useful for diagnosis and prognosis determination of cancers that can be classified into subgroups for prognosis of the cancer based on MAI. For example, MAI has been used successfully in the classification of malignant melanoma, ovarian cancer, bladder cancer, and prostatic adenocarcinoma. Thus, the methods and products of the invention also are applicable to non-breast cancers that can be classified by MAI.

The invention may also encompass cancers other than breast cancer, including but not limited to: biliary tract cancer; bladder cancer; brain cancer including glioblastomas and medulloblastomas; cervical cancer; choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; gastric cancer; hematological neoplasms including acute lymphocytic and myelogenous leukemia; multiple myeloma; AIDS-associated leukemias and adult T-cell leukemia lymphoma; intraepithelial neoplasms including Bowen's disease and Paget's disease; liver cancer; lung cancer; lymphomas including Hodgkin's disease and lymphocytic lymphomas; neuroblastomas; oral cancer including squamous cell carcinoma; ovarian cancer including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells; pancreatic cancer; prostate cancer; rectal cancer; sarcomas including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma, and osteosarcoma; skin cancer including melanoma, Kaposi's sarcoma, basocellular cancer, and squamous cell cancer; testicular cancer including germinal tumors such as seminoma, non-seminoma (teratomas, choriocarcinomas), stromal tumors, and germ cell tumors; thyroid cancer including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinoma and Wilms tumor.

As used herein, a subject is a human, non-human primate, cow, horse, pig, sheep, goat, dog, cat or rodent. In all embodiments human subjects are preferred. Preferably the subject is a human either suspected of having breast cancer, or having been diagnosed with breast cancer. In a preferred embodiment of the invention the cancer is pre-menopausal, lymph node–negative breast cancer. Methods for identifying subjects suspected of having breast cancer may include manual examination, biopsy, subject's family medical history,

subject's medical history, or a number of imaging technologies such as mammography, magnetic resonance imaging, magnetic resonance spectroscopy, or positron emission tomography. Diagnostic methods for breast cancer and the clinical delineation of breast cancer diagnoses are well-known to those of skill in the medical arts.

As used herein, breast tissue sample is tissue obtained from a breast tissue biopsy using methods well-known to those of ordinary skill in the related medical arts. The phrase "suspected of being cancerous" as used herein means a breast cancer tissue sample believed by one of ordinary skill in the medical arts to contain cancerous cells. Methods for obtaining the sample from the biopsy include gross apportioning of a mass, microdissection, laser-based microdissection, or other art-known cell-separation methods.

Because of the variability of the cell types in diseased-tissue biopsy material, and the variability in sensitivity of the diagnostic methods used, the sample size required for analysis may range from 1, 10, 50, 100, 200, 300, 500, 1000, 5000, 10,000, to 50,000 or more cells. The appropriate sample size may be determined based on the cellular composition and condition of the biopsy and the standard preparative steps for this determination and subsequent isolation of the nucleic acid for use in the invention are well known to one of ordinary skill in the art. An example of this, although not intended to be limiting, is that in some instances a sample from the biopsy may be sufficient for assessment of RNA expression without amplification, but in other instances the lack of suitable cells in a small biopsy region may require use of RNA conversion and/or amplification methods or other methods to enhance resolution of the nucleic acid molecules. Such methods, which allow use of limited biopsy materials, are well known to those of ordinary skill in the art and include, but are not limited to: direct RNA amplification, reverse transcription of RNA to cDNA, amplification of cDNA, or the generation of radio-labeled nucleic acids.

As used herein, the phrase "determining the expression of a set of nucleic acid molecules in the breast tissue" means identifying RNA transcripts in the tissue sample by analysis of nucleic acid or protein expression in the tissue sample. As used herein, "set" refers to a group of nucleic acid molecules that include 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, or 51 different nucleic acid sequences from the group of nucleic acid sequences numbered 1 through 51 in Table 1 (SEQ ID Nos: 1-51).

The expression of the set of nucleic acid molecules in the sample from the breast cancer patient can be compared to the expression of the set of nucleic acid molecules in a

sample of breast tissue that is non-cancerous. As used herein, non-cancerous breast tissue means tissue determined by one of ordinary skill in the medical art to have no evidence of breast cancer based on standard diagnostic methods including, but not limited to, histologic staining and microscopic analysis.

Nucleic acid markers for cancer are nucleic acid molecules that by their presence or absence indicate the presence of absence of breast cancer. In tissue, certain nucleic acid molecules are expressed at different levels depending on whether tissue is non-cancerous or cancerous. In cancerous tissue, nucleic acid molecule expression may be correlated with MAI prognostic analysis. As described herein, breast cancer nucleic acid markers were identified by evaluating the nucleic acid molecules present in breast tumor tissue samples and comparing expression levels of the nucleic acid molecules with MAI levels determined for the tissues. An aspect of the invention is that different nucleic acid molecules are expressed in breast cancers with different MAI levels (i.e., high MAI versus low MAI) and these expression variations are identifiable by nucleic acid expression analysis, such as microarray analysis or protein expression analysis. Some nucleic acids are more likely to be, in other words, are preferentially expressed in cancers with high MAI levels and other nucleic acids are preferentially expressed in cancers with low MAI levels. According to the invention, the correlation between the preferential expression of nucleic acid markers and MAI classification allows expression of nucleic acid markers to be used to directly categorize breast cancers as low MAI or high MAI. Thus, nucleic acid expression-based categorization of breast cancer (by measurement of nucleic acid or protein expression) as low or high MAI may be used by one of ordinary skill in the medical arts to select an appropriate treatment regimen based on a patient's specific breast cancer prognosis.

Hybridization methods for nucleic acids are well known to those of ordinary skill in the art (see, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York). The nucleic acid molecules from a breast cancer tissue sample hybridize under stringent conditions to nucleic acid markers expressed in breast cancer. In one embodiment the markers are sets of two or more of the nucleic acid molecules as set forth in SEQ ID NOs: 1 through 51.

The breast cancer nucleic acid markers disclosed herein are known genes and fragments thereof. It may be desirable to identify variants of those genes, such as allelic

variants or single nucleotide polymorphisms (SNPs) in tissues. Accordingly, methods for identifying breast cancer nucleic acid markers, including variants of the disclosed full-length cDNAs, genomic DNAs, and SNPs are also included in the invention. The methods include contacting a nucleic acid sample (such as a cDNA library, genomic library, genomic DNA isolate, etc.) with a nucleic acid probe or primer derived from one of SEQ ID NOs:1 through 51. The nucleic acid sample and the probe or primer hybridize to complementary nucleotide sequences of nucleic acids in the sample, if any are present, allowing detection of nucleic acids related to SEQ ID NOs: 1-51. Preferably the probe or primer is detectably labeled. The specific conditions, reagents, and the like can be selected by one of ordinary skill in the art to selectively identify nucleic acids related to sets of two or more of SEQ ID NOs:1 through 51. The isolated nucleic acid molecule can be sequenced according to standard procedures.

In addition to native nucleic acid markers (SEQ ID NOs:1-51), the invention also includes degenerate nucleic acids that include alternative codons to those present in the native materials. For example, serine residues are encoded by the codons TCA, AGT, TCC, TCG, TCT, and AGC. Each of the six codons is equivalent for the purposes of encoding a serine residue. Similarly, nucleotide sequence triplets that encode other amino acid residues include, but are not limited to: CCA, CCC, CCG, and CCT (proline codons); CGA, CGC, CGG, CGT, AGA, and AGG (arginine codons); ACA, ACC, ACG, and ACT (threonine codons); AAC and AAT (asparagine codons); and ATA, ATC, and ATT (isoleucine codons). Other amino acid residues may be encoded similarly by multiple nucleotide sequences. Thus, the invention embraces degenerate nucleic acids that differ from the biologically isolated nucleic acids in codon sequence due to the degeneracy of the genetic code.

The invention also provides modified nucleic acid molecules, which include additions, substitutions, and deletions of one or more nucleotides such as the allelic variants and SNPs described above. In preferred embodiments, these modified nucleic acid molecules and/or the polypeptides they encode retain at least one activity or function of the unmodified nucleic acid molecule and/or the polypeptides, such as hybridization, antibody binding, etc. In certain embodiments, the modified nucleic acid molecules encode modified polypeptides, preferably polypeptides having conservative amino acid substitutions . As used herein, a "conservative amino acid substitution" refers to an amino acid substitution which does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H;

(d) A, G; (e) S, T; (f) Q, N; and (g) E, D. The modified nucleic acid molecules are structurally related to the unmodified nucleic acid molecules and in preferred embodiments are sufficiently structurally related to the unmodified nucleic acid molecules so that the modified and unmodified nucleic acid molecules hybridize under stringent conditions known to one of skill in the art.

For example, modified nucleic acid molecules that encode polypeptides having single amino acid changes can be prepared for use in the methods and products disclosed herein. Each of these nucleic acid molecules can have one, two, or three nucleotide substitutions exclusive of nucleotide changes corresponding to the degeneracy of the genetic code as described herein. Likewise, modified nucleic acid molecules that encode polypeptides having two amino acid changes can be prepared, which have, e.g., 2-6 nucleotide changes. Numerous modified nucleic acid molecules like these will be readily envisioned by one of skill in the art, including for example, substitutions of nucleotides in codons encoding amino acids 2 and 3, 2 and 4, 2 and 5, 2 and 6, and so on. In the foregoing example, each combination of two amino acids is included in the set of modified nucleic acid molecules, as well as all nucleotide substitutions which code for the amino acid substitutions. Additional nucleic acid molecules that encode polypeptides having additional substitutions (i.e., 3 or more), additions or deletions [e.g., by introduction of a stop codon or a splice site(s)] also can be prepared and are embraced by the invention as readily envisioned by one of ordinary skill in the art. Any of the foregoing nucleic acids can be tested by routine experimentation for retention of structural relation to or activity similar to the nucleic acids disclosed herein.

In the invention, standard hybridization techniques of microarray technology are utilized to assess patterns of nucleic acid expression and identify nucleic acid marker expression. Microarray technology, which is also known by other names including: DNA chip technology, gene chip technology, and solid-phase nucleic acid array technology, is well known to those of ordinary skill in the art and is based on, but not limited to, obtaining an array of identified nucleic acid probes on a fixed substrate, labeling target molecules with reporter molecules (e.g., radioactive, chemiluminescent, or fluorescent tags such as fluorescein, Cye3-dUTP, or Cye5-dUTP), hybridizing target nucleic acids to the probes, and evaluating target-probe hybridization. A probe with a nucleic acid sequence that perfectly matches the target sequence will, in general, result in detection of a stronger reporter-molecule signal than will probes with less perfect matches. Many components and techniques utilized in nucleic acid microarray technology are presented in *The Chipping*

Forecast, Nature Genetics, Vol.21, Jan 1999, the entire contents of which is incorporated by reference herein.

According to the present invention, microarray substrates may include but are not limited to glass, silica, aluminosilicates, borosilicates, metal oxides such as alumina and nickel oxide, various clays, nitrocellulose, or nylon. In all embodiments a glass substrate is preferred. According to the invention, probes are selected from the group of nucleic acids including, but not limited to: DNA, genomic DNA, cDNA, and oligonucleotides; and may be natural or synthetic. Oligonucleotide probes preferably are 20 to 25-mer oligonucleotides and DNA/cDNA probes preferably are 500 to 5000 bases in length, although other lengths may be used. Appropriate probe length may be determined by one of ordinary skill in the art by following art-known procedures. In one embodiment, preferred probes are sets of two or more of the nucleic acid molecules set forth as SEQ ID NO: 1 through 51 (see also Table 1). Probes may be purified to remove contaminants using standard methods known to those of ordinary skill in the art such as gel filtration or precipitation.

In one embodiment, the microarray substrate may be coated with a compound to enhance synthesis of the probe on the substrate. Such compounds include, but are not limited to, oligoethylene glycols. In another embodiment, coupling agents or groups on the substrate can be used to covalently link the first nucleotide or olignucleotide to the substrate. These agents or groups may include, but are not limited to: amino, hydroxy, bromo, and carboxy groups. These reactive groups are preferably attached to the substrate through a hydrocarbyl radical such as an alkylene or phenylene divalent radical, one valence position occupied by the chain bonding and the remaining attached to the reactive groups. These hydrocarbyl groups may contain up to about ten carbon atoms, preferably up to about six carbon atoms. Alkylene radicals are usually preferred containing two to four carbon atoms in the principal chain. These and additional details of the process are disclosed, for example, in U.S. Patent 4,458,066, which is incorporated by reference in its entirety.

In one embodiment, probes are synthesized directly on the substrate in a predetermined grid pattern using methods such as light-directed chemical synthesis, photochemical deprotection, or delivery of nucleotide precursors to the substrate and subsequent probe production.

In another embodiment, the substrate may be coated with a compound to enhance binding of the probe to the substrate. Such compounds include, but are not limited to: polylysine, amino silanes, amino-reactive silanes (Chipping Forecast, 1999) or chromium

(Gwynne and Page, 2000). In this embodiment, presynthesized probes are applied to the substrate in a precise, predetermined volume and grid pattern, utilizing a computer-controlled robot to apply probe to the substrate in a contact-printing manner or in a non-contact manner such as ink jet or piezo-electric delivery. Probes may be covalently linked to the substrate with methods that include, but are not limited to, UV-irradiation. In another embodiment probes are linked to the substrate with heat.

Targets are nucleic acids selected from the group, including but not limited to: DNA, genomic DNA, cDNA, RNA, mRNA and may be natural or synthetic. In all embodiments, nucleic acid molecules from human breast tissue are preferred. The tissue may be obtained from a subject or may be grown in culture (e.g. from a breast cancer cell line).

In embodiments of the invention one or more control nucleic acid molecules are attached to the substrate. Preferably, control nucleic acid molecules allow determination of factors including but not limited to: nucleic acid quality and binding characteristics; reagent quality and effectiveness; hybridization success; and analysis thresholds and success. Control nucleic acids may include but are not limited to expression products of genes such as housekeeping genes or fragments thereof.

To select a set of tumor markers, the expression data generated by, for example, microarray analysis of gene expression, is preferably analyzed to determine which genes in different groups of cancer tissues are significantly differentially expressed. In the methods disclosed herein, the significance of gene expression was determined using Permax computer software, although any standard statistical package that can discriminate significant differences in expression may be used. Permax performs permutation 2-sample t-tests on large arrays of data. For high dimensional vectors of observations, the Permax software computes t-statistics for each attribute, and assesses significance using the permutation distribution of the maximum and minimum overall attributes. The main use is to determine the attributes (genes) that are the most different between two groups (e.g., high MAI tissues versus low MAI tissues), measuring "most different" using the value of the t-statistics, and their significance levels.

In one embodiment of the invention, expression of nucleic acid markers is used to select clinical treatment paradigms for breast cancer. Treatment options, as described herein, may include but are not limited to: chemotherapy, radiotherapy, adjuvant therapy, or any combination of the aforementioned methods. Aspects of treatment that may vary include, but are not limited to: dosages, timing of administration, or duration or therapy; and may or may

not be combined with other treatments, which may also vary in dosage, timing, or duration. Another treatment for breast cancer is surgery, which can be utilized either alone or in combination with any of the aforementioned treatment methods. One of ordinary skill in the medical arts may determine an appropriate treatment paradigm based on evaluation of differential expression of sets of two or more of the nucleic acid targets SEQ ID NOs:1-51. Cancers that express markers that are indicative of a more aggressive cancer or poor prognosis may be treated with more aggressive therapies.

Progression or regression of breast cancer is determined by comparison of two or more different breast cancer tissue samples taken at two or more different times from a subject. For example, progression or regression may be evaluated by assessments of expression of sets of two or more of the nucleic acid targets, including but not limited to SEQ ID NOs:1-51, in a breast cancer tissue sample from a subject before, during, and following treatment for breast cancer.

In another embodiment, novel pharmacological agents useful in the treatment of breast cancer can be identified by assessing variations in the expression of sets of two or more breast cancer nucleic acid markers, from among SEQ ID NOs:1-51, prior to and after contacting breast cancer cells or tissues with candidate pharmacological agents for the treatment of breast cancer. The cells may be grown in culture (e.g. from a breast cancer cell line), or may be obtained from a subject, (e.g. in a clinical trial of candidate pharmaceutical agents to treat breast cancer). Alterations in expression of two or more sets of breast cancer nucleic acid markers, from among SEQ ID NOs:1-51, in breast cancer cells or tissues tested before and after contact with a candidate pharmacological agent to treat breast cancer, indicate progression, regression, or stasis of the breast cancer thereby indicating efficacy of candidate agents and concomitant identification of lead compounds for therapeutic use in breast cancer.

The invention further provides efficient methods of identifying pharmacological agents or lead compounds for agents active at the level of breast cancer cellular function. Generally, the screening methods involve assaying for compounds that beneficially alter breast cancer nucleic acid molecule expression. Such methods are adaptable to automated, high throughput screening of compounds.

The assay mixture comprises a candidate pharmacological agent. Typically, a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a different response to the various concentrations. Typically, one of these concentrations

serves as a negative control, i.e., at zero concentration of agent or at a concentration of agent below the limits of assay detection. Candidate agents encompass numerous chemical classes, although typically they are organic compounds. Preferably, the candidate pharmacological agents are small organic compounds, i.e., those having a molecular weight of more than 50 yet less than about 2500, preferably less than about 1000 and, more preferably, less than about 500. Candidate agents comprise functional chemical groups necessary for structural interactions with polypeptides and/or nucleic acids, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups and more preferably at least three of the functional chemical groups. The candidate agents can comprise cyclic carbon or heterocyclic structure and/or aromatic or polyaromatic structures substituted with one or more of the above-identified functional groups. Candidate agents also can be biomolecules such as peptides, saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or structural analogs of the above, or combinations thereof and the like. Where the agent is a nucleic acid, the agent typically is a DNA or RNA molecule, although modified nucleic acids as defined herein are also contemplated.

Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides, synthetic organic combinatorial libraries, phage display libraries of random peptides, and the like. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural and synthetically produced libraries and compounds can be readily be modified through conventional chemical, physical, and biochemical means. Further, known pharmacological agents may be subjected to directed or random chemical modifications such as acylation, alkylation, esterification, amidification, etc. to produce structural analogs of the agents.

A variety of other reagents also can be included in the mixture. These include reagents such as salts, buffers, neutral proteins (e.g., albumin), detergents, etc. which may be used to facilitate optimal protein-protein and/or protein-nucleic acid binding. Such a reagent may also reduce non-specific or background interactions of the reaction components. Other reagents that improve the efficiency of the assay such as protease, inhibitors, nuclease inhibitors, antimicrobial agents, and the like may also be used.

The mixture of the foregoing assay materials is incubated under conditions whereby, the anti-breast cancer candidate agent specifically binds the cellular binding target, a portion thereof or analog thereof. The order of addition of components, incubation temperature, time of incubation, and other parameters of the assay may be readily determined. Such experimentation merely involves optimization of the assay parameters, not the fundamental composition of the assay. Incubation temperatures typically are between 4°C and 40°C. Incubation times preferably are minimized to facilitate rapid, high throughput screening, and typically are between 0.1 and 10 hours.

After incubation, the presence or absence of specific binding between the anti-breast cancer candidate agent and one or more binding targets is detected by any convenient method available to the user. For cell-free binding type assays, a separation step is often used to separate bound from unbound components. The separation step may be accomplished in a variety of ways. Conveniently, at least one of the components is immobilized on a solid substrate, from which the unbound components may be easily separated. The solid substrate can be made of a wide variety of materials and in a wide variety of shapes, e.g., microtiter plate, microbead, dipstick, resin particle, etc. The substrate preferably is chosen to maximize signal to noise ratios, primarily to minimize background binding, as well as for ease of separation and cost.

Separation may be effected for example, by removing a bead or dipstick from a reservoir, emptying or diluting a reservoir such as a microtiter plate well, rinsing a bead, particle, chromotograpic column or filter with a wash solution or solvent. The separation step preferably includes multiple rinses or washes. For example, when the solid substrate is a microtiter plate, the wells may be washed several times with a washing solution, which typically includes those components of the incubation mixture that do not participate in specific bindings such as salts, buffer, detergent, non-specific protein, etc. Where the solid substrate is a magnetic bead, the beads may be washed one or more times with a washing solution and isolated using a magnet.

Detection may be effected in any convenient way for cell-based assays such as two- or three-hybrid screens. The transcript resulting from a reporter gene transcription assay of the anti-cancer agent binding to a target molecule typically encodes a directly or indirectly detectable product, e.g., β-galactosidase activity, luciferase activity, and the like. For cell-free binding assays, one of the components usually comprises, or is coupled to, a detectable label. A wide variety of labels can be used, such as those that provide direct detection (e.g.,

radioactivity, luminescence, optical or electron density, etc). or indirect detection (e.g., epitope tag such as the FLAG epitope, enzyme tag such as horseseradish peroxidase, etc.). The label may be bound to an anti-cancer agent binding partner, or incorporated into the structure of the binding partner.

A variety of methods may be used to detect the label, depending on the nature of the label and other assay components. For example, the label may be detected while bound to the solid substrate or subsequent to separation from the solid substrate. Labels may be directly detected through optical or electron density, radioactive emissions, nonradiative energy transfers, etc. or indirectly detected with antibody conjugates, strepavidin-biotin conjugates, etc. Methods for detecting the labels are well known in the art.

The invention provides breast cancer gene-specific binding agents, methods of identifying and making such agents, and their use in diagnosis, therapy and pharmaceutical development. For example, breast cancer gene-specific pharmacological agents are useful in a variety of diagnostic and therapeutic applications as described herein. In general, the specificity of a breast cancer gene binding to a binding agent is shown by binding equilibrium constants. Targets which are capable of selectively binding a breast cancer gene preferably have binding equilibrium constants of at least about 10^7 M^{-1}, more preferably at least about 10^8 M^{-1}, and most preferably at least about 10^9 M^{-1}. The wide variety of cell based and cell free assays may be used to demonstrate breast cancer gene-specific binding. Cell-based assays include one, two and three hybrid screens, assays in which breast cancer gene-mediated transcription is inhibited or increased, etc. Cell-free assays include breast cancer gene-protein binding assays, immunoassays, etc. Other assays useful for screening agents which bind breast cancer polypeptides include fluorescence resonance energy transfer (FRET), and electrophoretic mobility shift analysis (EMSA).

In another aspect of the invention, pre- and post-treatment alterations in expression of two or more sets of breast cancer nucleic acid markers including, but not limited to, SEQ ID NOs:1-51 in breast cancer cells or tissues may be used to assess treatment parameters including, but not limited to: dosage, method of administration, timing of administration, and combination with other treatments as described herein.

Candidate pharmacological agents may include antisense oligonucleotides that selectively binds to a breast cancer nucleic acid marker molecule, as identified herein, to reduce the expression of the marker molecules in breast cancer cells and tissues. One of ordinary skill in the art can test of the effects of a reduction of expression of breast cancer

nucleic acid marker sequences *in vivo* or *in vitro*, to determine the efficacy of one or more antisense oligonucleotides.

As used herein, the term "antisense oligonucleotide" or "antisense" describes an oligonucleotide that is an oligoribonucleotide, oligodeoxyribonucleotide, modified oligoribonucleotide, or modified oligodeoxyribonucleotide which hybridizes under physiological conditions to DNA comprising a particular gene or to an mRNA transcript of that gene and, thereby, inhibits the transcription of that gene and/or the translation of that mRNA. The antisense molecules are designed so as to interfere with transcription or translation of a target gene upon hybridization with the target gene or transcript. Those skilled in the art will recognize that the exact length of the antisense oligonucleotide and its degree of complementarity with its target will depend upon the specific target selected, including the sequence of the target and the particular bases which comprise that sequence. It is preferred that the antisense oligonucleotide be constructed and arranged so as to bind selectively with the target under physiological conditions, i.e., to hybridize substantially more to the target sequence than to any other sequence in the target cell under physiological conditions.

Based upon the sequences of breast cancer expressed nucleic acids, or upon allelic or homologous genomic and/or cDNA sequences, one of skill in the art can easily choose and synthesize any of a number of appropriate antisense molecules for use in accordance with the present invention. In order to be sufficiently selective and potent for inhibition, such antisense oligonucleotides should comprise at least 10 and, more preferably, at least 15 consecutive bases that are complementary to the target, although in certain cases modified oligonucleotides as short as 7 bases in length have been used successfully as antisense oligonucleotides (Wagner et al., 1996). Most preferably, the antisense oligonucleotides comprise a complementary sequence of 20-30 bases. Although oligonucleotides may be chosen that are antisense to any region of the gene or mRNA transcripts, in preferred embodiments the antisense oligonucleotides correspond to N-terminal or 5' upstream sites such as translation initiation, transcription initiation or promoter sites. In addition, 3'-untranslated regions may be targeted. Targeting to mRNA splicing sites has also been used in the art but may be less preferred if alternative mRNA splicing occurs. In addition, the antisense is targeted, preferably, to sites in which mRNA secondary structure is not expected (see, e.g., Sainio et al., 1994) and at which proteins are not expected to bind. Finally, although the listed sequences are cDNA sequences, one of ordinary skill in the art may easily

derive the genomic DNA corresponding to the cDNA of a breast cancer expressed polypeptide. Thus, the present invention also provides for antisense oligonucleotides which are complementary to the genomic DNA corresponding to breast cancer expressed nucleic acids. Similarly, the use of antisense to allelic or homologous cDNAs and genomic DNAs are enabled without undue experimentation.

In one set of embodiments, the antisense oligonucleotides of the invention may be composed of "natural" deoxyribonucleotides, ribonucleotides, or any combination thereof. That is, the 5' end of one native nucleotide and the 3' end of another native nucleotide may be covalently linked, as in natural systems, via a phosphodiester internucleoside linkage. These oligonucleotides may be prepared by art-recognized methods, which may be carried out manually or by an automated synthesizer. They also may be produced recombinantly by vectors.

In preferred embodiments, however, the antisense oligonucleotides of the invention also may include "modified" oligonucleotides. That is, the oligonucleotides may be modified in a number of ways which do not prevent them from hybridizing to their target but which enhance their stability or targeting or which otherwise enhance their therapeutic effectiveness. The term "modified oligonucleotide" as used herein describes an oligonucleotide in which (1) at least two of its nucleotides are covalently linked via a synthetic internucleoside linkage (i.e., a linkage other than a phosphodiester linkage between the 5' end of one nucleotide and the 3' end of another nucleotide) and/or (2) a chemical group not normally associated with nucleic acids has been covalently attached to the oligonucleotide. Preferred synthetic internucleoside linkages are phosphorothioates, alkylphosphonates, phosphorodithioates, phosphate esters, alkylphosphonothioates, phosphoramidates, carbamates, carbonates, phosphate triesters, acetamidates, carboxymethyl esters, and peptides.

The term "modified oligonucleotide" also encompasses oligonucleotides with a covalently modified base and/or sugar. For example, modified oligonucleotides include oligonucleotides having backbone sugars that are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 3' position and other than a phosphate group at the 5' position. Thus modified oligonucleotides may include a 2'-O-alkylated ribose group. In addition, modified oligonucleotides may include sugars such as arabinose instead of ribose. The present invention, thus, contemplates pharmaceutical preparations containing modified antisense molecules that are complementary to and

hybridizable with, under physiological conditions, breast cancer expressed nucleic acids, together with pharmaceutically acceptable carriers.

Antisense oligonucleotides may be administered as part of a pharmaceutical composition. Such a pharmaceutical composition may include the antisense oligonucleotides in combination with any standard physiologically and/or pharmaceutically acceptable carriers which are known in the art. The compositions should be sterile and contain a therapeutically effective amount of the antisense oligonucleotides in a unit of weight or volume suitable for administration to a patient. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. The term "physiologically acceptable" refers to a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism. The characteristics of the carrier will depend on the route of administration. Physiologically and pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials, which are well known in the art.

Expression of breast cancer nucleic acid molecules can also be determined using protein measurement methods to determine expression of SEQ ID NOs:1-51, e.g., by determining the expression of polypeptides encoded by SEQ ID NOs:1-51 (SEQ ID NOs: 52-102, respectively). Preferred methods of specifically and quantitatively measuring proteins include, but are not limited to: mass spectroscopy-based methods such as surface enhanced laser desorption ionization (SELDI; e.g., Ciphergen ProteinChip System), non-mass spectroscopy-based methods, antibody-capture protein arrays and immunohistochemistry-based methods such as 2-dimensional gel electrophoresis.

SELDI methodology may be used, through procedures known to those of ordinary skill in the art, to vaporize microscopic amounts of tumor protein and to create a "fingerprint" of individual proteins, thereby allowing simultaneous measurement of the abundance of many proteins in a single sample. Preferably SELDI-based assays may be utilized to classify breast cancer tumors. Such assays preferably include, but are not limited to the following examples. Gene products discovered by RNA microarrays may be selectively measured by specific (antibody mediated) capture to the SELDI protein disc (e.g., selective SELDI). Gene products discovered by protein screening (e.g., with 2-D gels), may be resolved by "total protein SELDI" optimized to visualize those particular markers of interest from among SEQ ID NOs:1-51. Predictive models of tumor classification from SELDI measurement of multiple markers from among SEQ ID NOs:1-51 may be utilized for the SELDI strategies. In an

additional embodiment a set of primary lymph node-negative premenopausal breast cancer tissues may be preferably utilized to determine the risk classification of breast cancer based on SELDI results.

The invention also involves agents such as polypeptides that bind to breast cancer-associated polypeptides, i.e., SEQ ID NOs:52-102. Such binding agents can be used, for example, in screening assays to detect the presence or absence of breast cancer-associated polypeptides and complexes of breast cancer-associated polypeptides and their binding partners and in purification protocols to isolate breast cancer-associated polypeptides and complexes of breast cancer-associated polypeptides and their binding partners. Such agents also may be used to inhibit the native activity of the breast cancer-associated polypeptides, for example, by binding to such polypeptides.

The invention, therefore, embraces peptide binding agents which, for example, can be antibodies or fragments of antibodies having the ability to selectively bind to breast cancer-associated polypeptides. Antibodies include polyclonal and monoclonal antibodies, prepared according to conventional methodology.

Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W.R. (1986) The Experimental Foundations of Modern Immunology Wiley & Sons, Inc., New York; Roitt, I. (1991) Essential Immunology, 7th Ed., Blackwell Scientific Publications, Oxford). The pFc' and Fc regions, for example, are effectors of the complement cascade but are not involved in antigen binding. An antibody from which the pFc' region has been enzymatically cleaved, or which has been produced without the pFc' region, designated an $F(ab')_2$ fragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fc region has been enzymatically cleaved, or which has been produced without the Fc region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Proceeding further, Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity determining regions (CDRs), which directly interact with the epitope of the antigen, and framework regions (FRs), which maintain the tertiary structure of the

paratope (see, in general, Clark, 1986; Roitt, 1991). In both the heavy chain Fd fragment and the light chain of IgG immunoglobulins, there are four framework regions (FR1 through FR4) separated respectively by three complementarity determining regions (CDR1 through CDR3). The CDRs, and in particular the CDR3 regions, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a mammalian antibody may be replaced with similar regions of conspecific or heterospecific antibodies while retaining the epitopic specificity of the original antibody. This is most clearly manifested in the development and use of "humanized" antibodies in which non-human CDRs are covalently joined to human FR and/or Fc/pFc' regions to produce a functional antibody. See, e.g., U.S. patents 4,816,567, 5,225,539, 5,585,089, 5,693,762 and 5,859,205.

Fully human monoclonal antibodies also can be prepared by immunizing mice transgenic for large portions of human immunoglobulin heavy and light chain loci. Following immunization of these mice (e.g., XenoMouse (Abgenix), HuMAb mice (Medarex/GenPharm)), monoclonal antibodies can be prepared according to standard hybridoma technology. These monoclonal antibodies will have human immunoglobulin amino acid sequences and therefore will not provoke human anti-mouse antibody (HAMA) responses when administered to humans.

Thus, as will be apparent to one of ordinary skill in the art, the present invention also provides for $F(ab')_2$, Fab, Fv and Fd fragments; chimeric antibodies in which the Fc and/or FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric $F(ab')_2$ fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric Fab fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; and chimeric Fd fragment antibodies in which the FR and/or CDR1 and/or CDR2 regions have been replaced by homologous human or non-human sequences. The present invention also includes so-called single chain antibodies.

Thus, the invention involves polypeptides of numerous size and type that bind specifically to polypeptides selected from SEQ ID NOs:52-102, and complexes of both breast cancer-associated polypeptides and their binding partners. These polypeptides may be derived also from sources other than antibody technology. For example, such polypeptide binding agents can be provided by degenerate peptide libraries which can be readily prepared

in solution, in immobilized form or as phage display libraries. Combinatorial libraries also can be synthesized of peptides containing one or more amino acids. Libraries further can be synthesized of peptoids and non-peptide synthetic moieties.

Phage display can be particularly effective in identifying binding peptides useful according to the invention. Briefly, one prepares a phage library (using e.g. m13, fd, or lambda phage), displaying inserts from 4 to about 80 amino acid residues using conventional procedures. The inserts may represent, for example, a completely degenerate or biased array. One then can select phage-bearing inserts which bind to the breast cancer-associated polypeptide. This process can be repeated through several cycles of reselection of phage that bind to the breast cancer-associated polypeptide. Repeated rounds lead to enrichment of phage bearing particular sequences. DNA sequence analysis can be conducted to identify the sequences of the expressed polypeptides. The minimal linear portion of the sequence that binds to the breast cancer-associated polypeptide can be determined. One can repeat the procedure using a biased library containing inserts containing part or all of the minimal linear portion plus one or more additional degenerate residues upstream or downstream thereof. Yeast two-hybrid screening methods also may be used to identify polypeptides that bind to the breast cancer-associated polypeptides.

Thus, the breast cancer-associated polypeptides of the invention, including fragments thereof, can be used to screen peptide libraries, including phage display libraries, to identify and select peptide binding partners of the breast cancer-associated polypeptides of the invention. Such molecules can be used, as described, for screening assays, for purification protocols, for interfering directly with the functioning of breast cancer-associated polypeptides and for other purposes that will be apparent to those of ordinary skill in the art. For example, isolated breast cancer-associated polypeptides can be attached to a substrate (e.g., chromatographic media, such as polystyrene beads, a filter, or an array substrate), and then a solution suspected of containing the binding partner may be applied to the substrate. If a binding partner that can interact with breast cancer-associated polypeptides is present in the solution, then it will bind to the substrate-bound breast cancer-associated polypeptide. The binding partner then may be isolated.

As detailed herein, the foregoing antibodies and other binding molecules may be used for example, to identify tissues expressing protein or to purify protein. Antibodies also may be coupled to specific diagnostic labeling agents for imaging of cells and tissues that express breast cancer-associated polypeptides or to therapeutically useful agents according to

standard coupling procedures. Diagnostic agents include, but are not limited to, barium sulfate, iocetamic acid, iopanoic acid, ipodate calcium, diatrizoate sodium, diatrizoate meglumine, metrizamide, tyropanoate sodium and radiodiagnostics including positron emitters such as fluorine-18 and carbon-11, gamma emitters such as iodine-123, technitium-99m, iodine-131 and indium-111, nuclides for nuclear magnetic resonance such as fluorine and gadolinium.

The invention further includes protein microarrays for analyzing expression of breast cancer-associated peptides selected from SEQ ID NOs:52-102. In this aspect of the invention, standard techniques of microarray technology are utilized to assess expression of the breast cancer-associated polypeptides and/or identify biological constituents that bind such polypeptides. The constituents of biological samples include antibodies, lymphocytes (particularly T lymphocytes), and the like. Protein microarray technology, which is also known by other names including: protein chip technology and solid-phase protein array technology, is well known to those of ordinary skill in the art and is based on, but not limited to, obtaining an array of identified peptides or proteins on a fixed substrate, binding target molecules or biological constituents to the peptides, and evaluating such binding. See, e.g., G. MacBeath and S.L. Schreiber, "Printing Proteins as Microarrays for High-Throughput Function Determination," *Science* 289(5485):1760-1763, 2000.

Preferably antibodies or antigen binding fragments thereof that specifically bind polypeptides selected from the group consisting of SEQ ID NOs:52-102 are attached to the microarray substrate in accordance with standard attachment methods known in the art. These arrays can be used to quantify the expression of the polypeptides identified herein.

In some embodiments of the invention, one or more control peptide or protein molecules are attached to the substrate. Preferably, control peptide or protein molecules allow determination of factors such as peptide or protein quality and binding characteristics, reagent quality and effectiveness, hybridization success, and analysis thresholds and success.

The use of such methods to determine expression of breast cancer nucleic acids from among SEQ ID NOs:1-51 and/or proteins from among SEQ ID Nos:52-102 can be done with routine methods known to those of ordinary skill in the art and the expression determined by protein measurement methods may be correlated to MAI levels and used as a prognostic method for selecting treatment strategies for breast cancer patients.

Examples

Introduction

To establish a prognostic tool for designing breast cancer treatment regimens, expression patterns in primary breast cancer specimens were assessed and correlated with clinical outcome. Primary breast cancer tumors from premenopausal women with no lymph node metastases at the time of initial presentation were classified using the Mitotic Activity Index (MAI), which has been shown to predict disease-free survival in this type of disease. RNA was isolated, hybridized with Affymetrix HuFL human expression arrays, and analyzed to ascertain which genes discriminate the two groups.

Methods

Breast Cancers Used for RNA Microarray Expression Analysis

Primary frozen breast cancers from premenopausal women with no lymph node metastases at the time of initial presentation were assembled from material discarded following routine surgical removal for diagnostic purposes. Institutional review and human subjects approval for this project was obtained from Brigham and Women's Hospital. Fresh tissue was frozen in liquid nitrogen, and a single fragment split for confirmatory histology and RNA isolation. Individual fragments of frozen tumor tissues (estimated as 500 mg minimum) were split by fracturing under liquid nitrogen, and a portion processed for confirmatory histology using standard methods. The remaining tissue was used for synchronous RNA, protein, and DNA isolations with TRIzol reagents (Life Technologies, Inc., Rockville, MD) using standard methods. Only tumors where the actual frozen tissue contained >50% tumor cells were used.

Mitotic Activity Index

All tumors were classified by Mitotic Activity Index (Baak et al., 1989; van Diest et al., 1991; van Diest et al., 1992(a); Uyterlinde et al., 1990; van Diest et al., 1992(b); Jannink et al., 1996; Baak et al., 1992; Baak et al., 1993) using paraffin H&E stained tissues sections prepared for diagnostic purposes at the time of excision. The MAI is the total number of mitoses counted in 10 consecutive high-power fields (objective, x40; numeric aperture, 0.75; field diameter, 450 microns) in the most cellular area at the periphery of the tumor, with the subjectively highest mitotic activity (Jannink et al., 1995). Risk groups have previously been

defined using a threshold of 10 mitoses/unit area (Tosi et al., 1986; Jannink et al., 1995; Theissig et al., 1996). Tumors with MAI≥10 were assigned to the high risk group, and those with MAI≤3 to the low risk group.

Microarray Expression Analysis

RNA from 27 qualifying tumors was reverse transcribed and resultant cDNA used for *in vitro* transcriptional synthesis of fluorescently labeled nucleic acid probes which were then hybridized to Affymetrix HuFL human expression arrays (approximately 7100, probe sets, estimated 5800 unique genes). Hybridization images were analyzed with Affymetrix software to generate a data matrix of named probes by quantitative expression level in each tissue. RNA labeling, microarray hybridization, and microarray analysis were performed as per vendor's instructions for HuGeneFL array (Affymetrix, Santa Clara, CA). Four tumors were excluded from analysis because they failed to meet quality control criteria for microarray hybridization: 3 cases had low hybridization signal, one case had high background.

Results

Analysis of 23 primary breast cancer specimens from premenopausal lymph node negative women were split between two prognostic groups (Low MAI, MAI≤3, n=11 and High MAI, MAI≥10, n=12) and was accomplished as follows. Affymetrix HuFL expression values were normalized by scaling so the sum of AD (AD units are the quantitative expression units used by Affymetrix) values in each sample was 3,000,000; genes for which RNA abundance was absent or marginal were reset to a value of 0, then any values less than 20 were reset to 20. The result is the GPT datastate, which was then log transformed and discriminating genes selected by t-test comparison of the logged data between low and high MAI groups. Significance cutoffs for the t-tests used Permax <0.96 based on 10,000 random permutations of the data. Permax is a data analysis software tool for testing the significance of gene expression. It has been presented by Mutter, et al., 8th International Workshop on Chromosomes in Solid Tumors, Tucson, AZ, 2000; and is available online at biowww.dfci.harvard.edu/~gray/permax.html and from Robert J. Gray, Department of Biostatistical Science, Dana-Farber Cancer Institute, 44 Binney Street Boston, MA 02115. Permax details enclosed therein are incorporated by reference herein. Seventy eight of 7070 Affymetrix probe sets were selected by Permax.

Filters for minimum divergence between the average expression values of the two groups (Low vs. High MAI) were applied as follows: ratio of means ≥2, and difference between means ≥100. It was determined that 51/78 genes passed these filters. The final 51 selected genes which discriminate between low and high MAI subgroups appear in Table 1 and as SEQ ID NOs:1-51. Average expression in high MAI tumors and low MAI tumors is shown as HX and LX, respectively.

Table 1. Gene list identifying 51 genes that discriminate low from high MAI breast cancers.

SEQ ID NO	Short Name	GenBank Acc.No.	Permax	HX	LX	FOLDABS	DIFFABS
1	ABCB2	X57522	0.9577	501	83	6.0	417
2	ACTA2	X13839	0.7131	3098	6152	2.0	3054
3	AMD1	M21154	0.0808	257	50	5.1	207
4	APM2	D45370	0.3317	590	2682	4.5	2092
5	ASAH	U70063	0.8435	360	990	2.8	630
6	BARD1	U76638	0.5637	242	102	2.4	140
7	CCNH	U11791	0.9104	104	204	2.0	100
8	CCT2	U91327	0.8801	280	109	2.6	171
9	CDC20	U05340	0.0669	579	20	29.0	559
10	CDC34	L22005	0.6979	182	41	4.4	141
11	CDKN3	U02681	0.0072	454	63	7.2	391
12	CKS1	X54941	0.8823	539	219	2.5	320
13	CKS2	X54942	0.1881	413	119	3.5	294
14	COX7A1	M83186	0.9223	89	326	3.6	236
15	CPA3	M73720	0.8234	132	357	2.7	225
16	CPE	X51405	0.1984	80	243	3.0	163
17	CX3CR1	U20350	0.0317	70	328	4.7	258
18	DLG4	U83192	0.3427	20	179	8.9	159
19	DOC1	U53445	0.927	122	276	2.3	154
20	DXS9879E	X92896	0.9448	744	331	2.3	413
21	E2-EPF	M91670	0.9602	324	20	16.2	304
22	ElastinAlt2	U77846	0.8368	417	2210	5.3	1792
23	GTF2A1	U14193	0.7495	528	249	2.1	279
24	GUA5MPST	U10860	0.6129	599	114	5.2	485
25	H2AFX	X14850	0.8106	496	193	2.6	303
26	H2BFA	M60750	0.2334	508	143	3.6	365
27	Hevin	X86693	0.7484	529	1686	3.2	1157
28	HNRPH2	U01923	0.9056	106	231	2.2	126
29	HPV16E1Bind	U96131	0.2439	194	78	2.5	116
30	IDUA	M74715	0.1712	176	594	3.4	418
31	IGF1	X57025	0.9213	79	265	3.4	186
32	IQGAP2	U51903	0.9517	137	321	2.3	184
33	ISG15	M13755	0.9316	2133	386	5.5	1747
34	JAG1	U61276	0.9466	79	264	3.3	185
35	LAMA2	Z26653	0.8882	31	213	6.8	182
36	LAMB2	X79683	0.083	156	658	4.2	502
37	LBR	L25931	0.5991	221	68	3.2	153
38	MMP2	M55593	0.93	1765	3670	2.1	1905
39	MMSDH	M93405	0.9072	297	669	2.3	372
40	MYH11	AF001548	0.3109	164	777	4.7	612
41	MYLK	U48959	0.8351	158	680	4.3	522
42	PDE4A	L20965	0.8912	34	176	5.2	142
43	SCNN1A	X76180	0.694	352	864	2.5	511
44	SCYB10	X02530	0.4416	528	83	6.4	445
45	SNRPB	X17567	0.8965	1473	638	2.3	835
46	STAT1	M97936	0.9553	440	20	22.0	420
47	TAF2A	X07024	0.6819	193	65	2.9	127
48	TCEAL1	M99701	0.5595	241	749	3.1	508
49	TPM1	Z24727	0.5676	1266	2533	2.0	1267
50	TPS2	M33493	0.3638	194	892	4.6	698
51	UBCH10	U73379	0.1972	1519	639	2.4	880

Several features of selected genes provide reassurance that low frequency random events were not the cause of expression differences between groups. A review of the 51 selected genes (Table 1) shows that five pairs of genes known to be co-expressed were selected independently (two carboxypeptidases, two histones, two cdc28, two ubiquitins, two laminins, and myosin/tropomyosin), and reciprocal regulation of ligand and receptor, a common regulatory pattern, occurred once (laminin and lamin receptor) amongst genes selected.

The first expectation is that genes whose expression is linked to cell division would be represented in this comparison of tumors whose mitotic activity differs systematically. This was in fact the largest category of selected genes, with expression of 11/12 cell cycle genes greatest in the high MAI group. Genes which are preferentially expressed (at higher levels) in the low MAI group include those encoding extracellular matrix or enzymes which may remodel extracellular matrix (proteolytic enzymes).

The gene expression data presented in Table 1 can be used to generate an expression matrix of 51 selected genes by 23 tissues examined. Using standard clustering algorithms, dendrograms can be provided on the borders of the matrix (e.g., using Wards linkage and Euclidean distance) to show cluster relationships between tissues and genes. Similarly, a gene expression matrix can be generated using data normalized by standard deviation for each gene [STD(GPT)]. Dendrograms on borders of the matrix can be provided to show cluster relationships between tissues and genes. In this type of matrix, clustering of genes is based upon relative changes without bias due to absolute expression level, because each gene is expressed in standard deviation from the mean for that specific gene. However, unlike the other expression matrix described above, the absolute magnitude of expression cannot be directly inferred from this plot.

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The present invention is not limited in scope by the examples provided, since the examples are intended as illustrations of various aspects of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown are described herein will become apparent to those skilled in the art for the foregoing description and fall within the scope of the appended claims. The advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention. All references, patents, and patent publications that are recited in this application are incorporated in their entirety herein by reference.

We claim:

Claims

1. A method for diagnosing breast cancer in a subject suspected of having breast cancer comprising:

obtaining from the subject a breast tissue sample suspected of being cancerous,

determining the expression of a set of nucleic acid molecules or expression products thereof in the breast tissue sample, wherein the set of nucleic acid molecules comprises at least two nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

2. The method of claim 1, wherein the set of nucleic acid molecules comprises at least 3 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

3. The method of claim 1, wherein the set includes at least 4 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

4. The method of claim 1, wherein the set includes at least 5 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

5. The method of claim 1, wherein the set includes at least 10 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

6. The method of claim 1, wherein the set includes at least 15 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

7. The method of claim 1, wherein the set includes at least 20 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

8. The method of claim 1, wherein the set includes at least 30 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

9. The method of claim 1, wherein the set includes at least 40 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

10. The method of claim 1, further comprising:

determining the expression of the set of nucleic acid molecules or expression products thereof in a non-cancerous breast tissue sample, and comparing the expression of the set of nucleic acid molecules or expression products thereof in the breast tissue sample suspected of being cancerous and the non-cancerous breast tissue sample.

11. A method for identifying a set of nucleic acid markers or expression products thereof effective for determining the prognosis of cancer, comprising:

obtaining a plurality of tumor tissue samples from a plurality of subjects afflicted with cancer,

classifying the plurality of tumor tissue samples according to mitotic activity index (MAI) into high MAI and low MAI groups,

determining differences in the expression of a plurality of nucleic acid molecules or expression products thereof in the tumor tissue samples, and

selecting as a set of nucleic acid markers the nucleic acid molecules or expression products thereof which are differentially expressed in the high MAI and the low MAI groups,

wherein the set of nucleic acid markers or expression products thereof effective for determining poor prognosis of cancer comprises one or more nucleic acid molecules or expression products thereof which are preferentially expressed in high MAI tumor tissue samples, and wherein the set of nucleic acid markers or expression products thereof effective for determining good prognosis of cancer comprises one or more nucleic acid molecules or expression products thereof which are preferentially expressed in low MAI tumor tissue samples.

12. The method of claim 11, wherein the cancer is breast cancer.

13. The method of claim 11, wherein the differences in the expression of a plurality of nucleic acid molecules are determined by a method selected from the group consisting of nucleic acid hybridization and nucleic acid amplification.

14. The method of claim 13, wherein the nucleic acid hybridization is performed using a solid-phase nucleic acid molecule array.

15. A method for selecting a course of treatment of a subject having or suspected of having cancer, comprising:

obtaining from the subject a tissue sample suspected of being cancerous,

determining the expression of a set of nucleic acid markers or expression products thereof which are differentially expressed in high MAI tumor tissue samples to determine the MAI of the tissue sample of the subject, and

selecting a course of treatment appropriate to the cancer of the subject.

16. The method of claim 15 wherein the cancer is breast cancer.

17. The method of claim 16, further comprising:

determining the expression of a set of nucleic acid markers that are differentially expressed in low MAI breast tumor tissue samples.

18. The method of claim 15, wherein the expression of a set of nucleic acid markers is determined by a method selected from the group consisting of nucleic acid hybridization and nucleic acid amplification.

19. The method of claim 18, wherein the nucleic acid hybridization is performed using a solid-phase nucleic acid molecule array.

20. A method for evaluating treatment of cancer, comprising:

obtaining a first determination of the expression of a set of nucleic acid molecules or expression products thereof, which are differentially expressed in high MAI tumor tissue samples to determine the MAI of the tissue sample from a subject undergoing treatment for cancer,

obtaining a second determination of the expression of a set of nucleic acid molecules or expression products thereof, which are differentially expressed in high MAI tumor tissue samples to determine the MAI of the second tissue sample from the subject after obtaining the first determination,

comparing the first determination of expression to the second determination of expression as an indication of evaluation of the treatment.

21. The method of claim 20, wherein the cancer is breast cancer.

22. The method of claim 21, further comprising:

determining the expression of a set of nucleic acid markers which are differentially expressed in low MAI breast tumor tissue samples.

23. The method of claim 20, wherein the expression of a set of nucleic acid markers is determined by a method selected from the group consisting of nucleic acid hybridization and nucleic acid amplification.

24. The method of claim 20, wherein the nucleic acid hybridization is performed using a solid-phase nucleic acid molecule array.

25. A solid-phase nucleic acid molecule array consisting essentially of at least two nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51 fixed to a solid substrate.

26. The solid-phase nucleic acid molecule array of claim 24, further comprising at least one control nucleic acid molecule.

27. The solid-phase nucleic acid molecule array of claim 24, wherein the set of nucleic acid molecules comprises at least 3 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

28. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 4 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

29. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 5 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

30. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 10 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

31. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 15 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

32. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 20 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

33. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 30 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

34. The solid-phase nucleic acid molecule array of claim 24, wherein the set includes at least 40 nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51.

35. The solid-phase nucleic acid molecule array of claim 24, wherein the solid substrate comprises a material selected from the group consisting of glass, silica, aluminosilicates, borosilicates, metal oxides such as alumina and nickel oxide, various clays, nitrocellulose, and nylon.

36. The solid-phase nucleic acid molecule array of claim 24, wherein the nucleic acid molecules are fixed to the solid substrate by covalent bonding.

37. A solid-phase protein microarray comprising at least two antibodies or antigen-binding fragments thereof, that specifically bind at least two different polypeptides selected from the group consisting of SEQ ID NOs:52-102, fixed to a solid substrate.

38. The protein microarray of claim 37, wherein the microarray further comprises an antibody or antigen-binding fragment thereof, that binds specifically to a cancer-associated polypeptide other than those selected from the group consisting of SEQ ID NOs:52-102.

39. The protein microarray of claim 38, wherein the cancer-associated polypeptide other than those selected from the group consisting of SEQ ID NOs:52-102 is a breast cancer associated polypeptide.

40. The protein microarray of claim 37, further comprising at least one control polypeptide molecule.

41. The protein microarray of claim 37, wherein the antibodies are monoclonal or polyclonal antibodies.

42. The protein microarray of claim 37, wherein the antibodies are chimeric, human, or humanized antibodies.

43. The protein microarray of claim 37, wherein the antibodies are single chain antibodies.

44. The protein microarray of claim 37, wherein the antigen-binding fragments are $F(ab')_2$, Fab, Fd, or Fv fragments.

45. A method for identifying lead compounds for a pharmacological agent useful in the treatment of breast cancer, comprising:

contacting a breast cancer cell or tissue with a candidate pharmacological agent,

determining the expression of a set of nucleic acid molecules in the breast cancer cell or tissue sample under conditions which, in the absence of the candidate pharmacological agent, permit a first amount of expression of the set of nucleic acid molecules wherein the set of nucleic acid molecules comprises at least two nucleic acid molecules selected from the group consisting of SEQ ID NOs:1-51, and

detecting a test amount of the expression of the set of nucleic acid molecules, wherein a decrease in the test amount of expression in the presence of the candidate pharmacological agent relative to the first amount of expression indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which is useful in the treatment of breast cancer.

46. The method of claim 45, wherein the set of nucleic acid molecules is differentially expressed in high MAI breast tumor tissue samples.

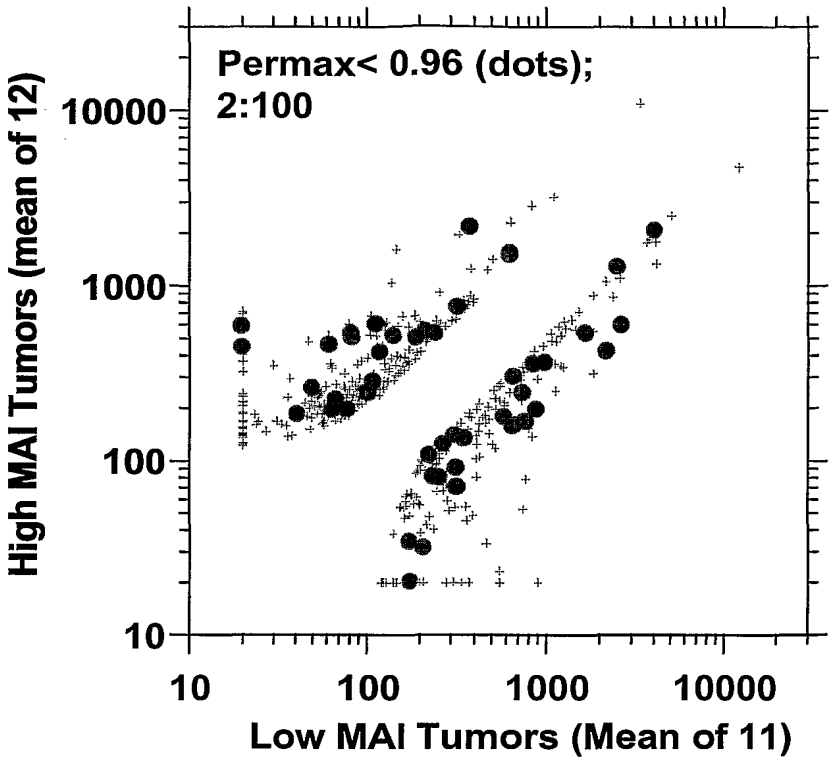
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Fig. 1

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Arg Pro Gly Arg Asp Arg Asp Gly Val Arg Val Pro Met Ala Ser Ser
    50                  55                  60

Arg Cys Pro Ala Pro Arg Gly Cys Arg Cys Leu Pro Gly Ala Ser Leu
65                  70                  75                  80

Ala Trp Leu Gly Thr Val Leu Leu Leu Leu Ala Asp Trp Val Leu Leu
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Arg Thr Ala Leu Pro Arg Ile Phe Ser Leu Leu Val Pro Thr Ala Leu
            100                 105                 110

Pro Leu Leu Arg Val Trp Ala Val Gly Leu Ser Arg Trp Ala Val Leu
        115                 120                 125

Trp Leu Gly Ala Cys Gly Val Leu Arg Ala Thr Val Gly Ser Lys Ser
    130                 135                 140

Glu Asn Ala Gly Ala Gln Gly Trp Leu Ala Ala Leu Lys Pro Leu Ala
145                 150                 155                 160

Ala Ala Leu Gly Leu Ala Leu Pro Gly Leu Ala Leu Phe Arg Glu Leu
                165                 170                 175

Ile Ser Trp Gly Ala Pro Gly Ser Ala Asp Ser Thr Arg Leu Leu His
            180                 185                 190

Trp Gly Ser His Pro Thr Ala Phe Val Val Ser Tyr Ala Ala Ala Leu
        195                 200                 205

Pro Ala Ala Ala Leu Trp His Lys Leu Gly Ser Leu Trp Val Pro Gly
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Gly Gln Gly Gly Ser Gly Asn Pro Val Arg Arg Leu Leu Gly Cys Leu
225                 230                 235                 240

Gly Ser Glu Thr Arg Arg Leu Ser Leu Phe Leu Val Leu Val Val Leu
                245                 250                 255

Ser Ser Leu Gly Glu Met Ala Ile Pro Phe Phe Thr Gly Arg Leu Thr
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Asp Trp Ile Leu Gln Asp Gly Ser Ala Asp Thr Phe Thr Arg Asn Leu
        275                 280                 285

Thr Leu Met Ser Ile Leu Thr Ile Ala Ser Ala Val Leu Glu Phe Val
    290                 295                 300

Gly Asp Gly Ile Tyr Asn Asn Thr Met Gly His Val His Ser His Leu
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Ser Thr Leu Ser Asp Ser Leu Ser Glu Asn Leu Ser Leu Phe Leu Trp
        355                 360                 365

Tyr Leu Val Arg Gly Leu Cys Leu Leu Gly Ile Met Leu Trp Gly Ser
    370                 375                 380

Val Ser Leu Thr Met Val Thr Leu Ile Thr Leu Pro Leu Leu Phe Leu
385                 390                 395                 400

Leu Pro Lys Lys Val Gly Lys Trp Tyr Gln Leu Leu Glu Val Gln Val
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Arg Glu Ser Leu Ala Lys Ser Ser Gln Val Ala Ile Glu Ala Leu Ser
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Ala Met Pro Thr Val Arg Ser Phe Ala Asn Glu Glu Gly Glu Ala Gln
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Lys Phe Arg Glu Lys Leu Gln Glu Ile Lys Thr Leu Asn Gln Lys Glu
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Ala Val Ala Tyr Ala Val Asn Ser Trp Thr Thr Ser Ile Ser Gly Met
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Leu Leu Lys Val Gly Ile Leu Tyr Ile Gly Gly Gln Leu Val Thr Ser
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Gly Ala Val Ser Ser Gly Asn Leu Val Thr Phe Val Leu Tyr Gln Met
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Gln Phe Thr Gln Ala Val Glu Val Leu Leu Ser Ile Tyr Pro Arg Val
        515                 520                 525

Gln Lys Ala Val Gly Ser Ser Glu Lys Ile Phe Glu Tyr Leu Asp Arg
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Thr Pro Arg Cys Pro Pro Ser Gly Leu Leu Thr Pro Leu His Leu Glu
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Gly Leu Val Gln Phe Gln Asp Val Ser Phe Ala Tyr Pro Asn Arg Pro
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Asp Val Leu Val Leu Gln Gly Leu Thr Phe Thr Leu Arg Pro Gly Glu
            580                 585                 590

Val Thr Ala Leu Val Gly Pro Asn Gly Ser Gly Lys Ser Thr Val Ala
        595                 600                 605

Ala Leu Leu Gln Asn Leu Tyr Gln Pro Thr Gly Gly Gln Leu Leu Leu
    610                 615                 620

Asp Gly Lys Pro Leu Pro Gln Tyr Glu His Arg Tyr Leu His Arg Gln
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Thr Ala Ala Ala Val Lys Ser Gly Ala His Ser Phe Ile Ser Gly Leu
        675                 680                 685

Pro Gln Gly Tyr Asp Thr Glu Val Asp Glu Ala Gly Ser Gln Leu Ser
    690                 695                 700

Gly Gly Gln Arg Gln Ala Val Ala Leu Ala Arg Ala Leu Ile Arg Lys
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Pro Cys Val Leu Ile Leu Asp Asp Ala Thr Ser Ala Leu Asp Ala Asn
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Ser Gln Leu Gln Val Glu Gln Leu Leu Tyr Glu Ser Pro Glu Arg Tyr
            740                 745                 750

Ser Arg Ser Val Leu Leu Ile Thr Gln His Leu Ser Leu Val Glu Gln
        755                 760                 765

Ala Asp His Ile Leu Phe Leu Glu Gly Gly Ala Ile Arg Glu Gly Gly
    770                 775                 780

Thr His Gln Gln Leu Met Glu Lys Lys Gly Cys Tyr Trp Ala Met Val
785                 790                 795                 800

Gln Ala Pro Ala Asp Ala Pro Glu
                805
```

<210> 53
<211> 377
<212> PRT
<213> Homo Sapiens

<400> 53

```
Met Cys Glu Glu Glu Asp Ser Thr Ala Leu Val Cys Asp Asn Gly Ser
1               5                   10                  15

Gly Leu Cys Lys Ala Gly Phe Ala Gly Asp Asp Ala Pro Arg Ala Val
            20                  25                  30

Phe Pro Ser Ile Val Gly Arg Pro Arg His Gln Gly Val Met Val Gly
        35                  40                  45

Met Gly Gln Lys Asp Ser Tyr Val Gly Asp Glu Ala Gln Ser Lys Arg
    50                  55                  60

Gly Ile Leu Thr Leu Lys Tyr Pro Ile Glu His Gly Ile Ile Thr Asn
65                  70                  75                  80

Trp Asp Asp Met Glu Lys Ile Trp His His Ser Phe Tyr Asn Glu Leu
                85                  90                  95

Arg Val Ala Pro Glu Glu His Pro Thr Leu Leu Thr Glu Ala Pro Leu
            100                 105                 110
```

```
Asn Pro Lys Ala Asn Arg Glu Lys Met Thr Gln Ile Met Phe Glu Thr
        115                 120                 125

Phe Asn Val Pro Ala Met Tyr Val Ala Ile Gln Ala Val Leu Ser Leu
    130                 135                 140

Tyr Ala Ser Gly Arg Thr Thr Gly Ile Val Leu Asp Ser Gly Asp Gly
145                 150                 155                 160

Val Thr His Asn Val Pro Ile Tyr Glu Gly Tyr Ala Leu Pro His Ala
                165                 170                 175

Ile Met Arg Leu Asp Leu Ala Gly Arg Asp Leu Thr Asp Tyr Leu Met
            180                 185                 190

Lys Ile Leu Thr Glu Arg Gly Tyr Ser Phe Val Thr Thr Ala Glu Arg
        195                 200                 205

Glu Ile Val Arg Asp Ile Lys Glu Lys Leu Cys Tyr Val Ala Leu Asp
    210                 215                 220

Phe Glu Asn Glu Met Ala Thr Ala Ala Ser Ser Ser Ser Leu Glu Lys
225                 230                 235                 240

Ser Tyr Glu Leu Pro Asp Gly Gln Val Ile Thr Ile Gly Asn Glu Arg
                245                 250                 255

Phe Arg Cys Pro Glu Thr Leu Phe Gln Pro Ser Phe Ile Gly Met Glu
            260                 265                 270

Ser Ala Gly Ile His Glu Thr Thr Tyr Asn Ser Ile Met Lys Cys Asp
        275                 280                 285

Ile Asp Ile Arg Lys Asp Leu Tyr Ala Asn Asn Val Leu Ser Gly Gly
    290                 295                 300

Thr Thr Met Tyr Pro Gly Ile Ala Asp Arg Met Gln Lys Glu Ile Thr
305                 310                 315                 320

Ala Leu Ala Pro Ser Thr Met Lys Ile Lys Ile Ile Ala Pro Pro Glu
                325                 330                 335

Arg Lys Tyr Ser Val Trp Ile Gly Gly Ser Ile Leu Ala Ser Leu Ser
            340                 345                 350

Thr Phe Gln Gln Met Trp Ile Ser Lys Gln Glu Tyr Asp Glu Ala Gly
        355                 360                 365

Pro Ser Ile Val His Arg Lys Cys Phe
    370                 375
```

<210> 54
<211> 334
<212> PRT
<213> Homo Sapiens

<400> 54

```
Met Glu Ala Ala His Phe Phe Glu Gly Thr Glu Lys Leu Leu Glu Val
```

```
1               5                   10                  15

Trp Phe Ser Arg Gln Gln Pro Asp Ala Asn Gln Gly Ser Gly Asp Leu
            20                  25                  30

Arg Thr Ile Pro Arg Ser Glu Trp Asp Ile Leu Leu Lys Asp Val Gln
        35                  40                  45

Cys Ser Ile Ile Ser Val Thr Lys Thr Asp Lys Gln Glu Ala Tyr Val
    50                  55                  60

Leu Ser Glu Ser Ser Met Phe Val Ser Lys Arg Arg Phe Ile Leu Lys
65                  70                  75                  80

Thr Cys Gly Thr Thr Leu Leu Leu Lys Ala Leu Val Pro Leu Leu Lys
                85                  90                  95

Leu Ala Arg Asp Tyr Ser Gly Phe Asp Ser Ile Gln Ser Phe Phe Tyr
            100                 105                 110

Ser Arg Lys Asn Phe Met Lys Pro Ser His Gln Gly Tyr Pro His Arg
        115                 120                 125

Asn Phe Gln Glu Glu Ile Glu Phe Leu Asn Ala Ile Phe Pro Asn Gly
    130                 135                 140

Ala Gly Tyr Cys Met Gly Arg Met Asn Ser Asp Cys Trp Tyr Leu Tyr
145                 150                 155                 160

Thr Leu Asp Phe Pro Glu Ser Arg Val Ile Ser Gln Pro Asp Gln Thr
                165                 170                 175

Leu Glu Ile Leu Met Ser Glu Leu Asp Pro Ala Val Met Asp Gln Phe
            180                 185                 190

Tyr Met Lys Asp Gly Val Thr Ala Lys Asp Val Thr Arg Glu Ser Gly
        195                 200                 205

Ile Arg Asp Leu Ile Pro Gly Ser Val Ile Asp Ala Thr Met Phe Asn
    210                 215                 220

Pro Cys Gly Tyr Ser Met Asn Gly Met Lys Ser Asp Gly Thr Tyr Trp
225                 230                 235                 240

Thr Ile His Ile Thr Pro Glu Pro Glu Phe Ser Tyr Val Ser Phe Glu
                245                 250                 255

Thr Asn Leu Ser Gln Thr Ser Tyr Asp Asp Leu Ile Arg Lys Val Val
            260                 265                 270

Glu Val Phe Lys Pro Gly Lys Phe Val Thr Thr Leu Phe Val Asn Gln
        275                 280                 285

Ser Ser Lys Cys Arg Thr Val Leu Ala Ser Pro Gln Lys Ile Glu Gly
    290                 295                 300

Phe Lys Arg Leu Asp Cys Gln Ser Ala Met Phe Asn Asp Tyr Asn Phe
305                 310                 315                 320

Val Phe Thr Ser Phe Ala Lys Lys Gln Gln Gln Gln Gln Ser
```

325 330

<210> 55
<211> 76
<212> PRT
<213> Homo Sapiens

<400> 55

Met Ala Ser Lys Gly Leu Gln Asp Leu Lys Gln Gln Val Glu Gly Thr
1 5 10 15

Ala Gln Glu Ala Val Ser Ala Ala Gly Ala Ala Ala Gln Gln Val Val
20 25 30

Asp Gln Ala Thr Glu Ala Gly Gln Lys Ala Met Asp Gln Leu Ala Lys
35 40 45

Thr Thr Gln Glu Thr Ile Asp Lys Thr Ala Asn Gln Ala Ser Asp Thr
50 55 60

Phe Ser Gly Ile Gly Lys Lys Phe Gly Leu Leu Lys
65 70 75

<210> 56
<211> 395
<212> PRT
<213> Homo Sapiens

<400> 56

Met Pro Gly Arg Ser Cys Val Ala Leu Val Leu Leu Ala Ala Ala Val
1 5 10 15

Ser Cys Ala Val Ala Gln His Ala Pro Pro Trp Thr Glu Asp Cys Arg
20 25 30

Lys Ser Thr Tyr Pro Pro Ser Gly Pro Thr Tyr Arg Gly Ala Val Pro
35 40 45

Trp Tyr Thr Ile Asn Leu Asp Leu Pro Pro Tyr Lys Arg Trp His Glu
50 55 60

Leu Met Leu Asp Lys Ala Pro Met Leu Lys Val Ile Val Asn Ser Leu
65 70 75 80

Lys Asn Met Ile Asn Thr Phe Val Pro Ser Gly Lys Val Met Gln Val
85 90 95

Val Asp Glu Lys Leu Pro Gly Leu Leu Gly Asn Phe Pro Gly Pro Phe
100 105 110

Glu Glu Glu Met Lys Gly Ile Ala Ala Val Thr Asp Ile Pro Leu Gly
115 120 125

Glu Ile Ile Ser Phe Asn Ile Phe Tyr Glu Leu Phe Thr Ile Cys Thr
130 135 140

Ser Ile Val Ala Glu Asp Lys Lys Gly His Leu Ile His Gly Arg Asn
145 150 155 160

```
Met Asp Phe Gly Val Phe Leu Gly Trp Asn Ile Asn Asn Asp Thr Trp
                165                 170                 175

Val Ile Thr Glu Gln Leu Lys Pro Leu Thr Val Asn Leu Asp Phe Gln
            180                 185                 190

Arg Asn Asn Lys Thr Val Phe Lys Ala Ser Ser Phe Ala Gly Tyr Val
        195                 200                 205

Gly Met Leu Thr Gly Phe Lys Pro Gly Leu Phe Ser Leu Thr Leu Asn
    210                 215                 220

Glu Arg Phe Ser Ile Asn Gly Gly Tyr Leu Gly Ile Leu Glu Trp Ile
225                 230                 235                 240

Leu Gly Lys Lys Asp Ala Met Trp Ile Gly Phe Leu Thr Arg Thr Val
                245                 250                 255

Leu Glu Asn Ser Thr Ser Tyr Glu Glu Ala Lys Asn Leu Leu Thr Lys
            260                 265                 270

Thr Lys Ile Leu Ala Pro Ala Tyr Phe Ile Leu Gly Gly Asn Gln Ser
        275                 280                 285

Gly Glu Gly Cys Val Ile Thr Arg Asp Arg Lys Glu Ser Leu Asp Val
    290                 295                 300

Tyr Glu Leu Asp Ala Lys Gln Gly Arg Trp Tyr Val Val Gln Thr Asn
305                 310                 315                 320

Tyr Asp Arg Trp Lys His Pro Phe Phe Leu Asp Asp Arg Arg Thr Pro
                325                 330                 335

Ala Lys Met Cys Leu Asn Arg Thr Ser Gln Glu Asn Ile Ser Phe Glu
            340                 345                 350

Thr Met Tyr Asp Val Leu Ser Thr Lys Pro Val Leu Asn Lys Leu Thr
        355                 360                 365

Val Tyr Thr Thr Leu Ile Asp Val Thr Lys Gly Gln Phe Glu Thr Tyr
    370                 375                 380

Leu Arg Asp Cys Pro Asp Pro Cys Ile Gly Trp
385                 390                 395

<210>  57
<211>  777
<212>  PRT
<213>  Homo Sapiens

<400>  57

Met Pro Asp Asn Arg Gln Pro Arg Asn Arg Gln Pro Arg Ile Arg Ser
1               5                   10                  15

Gly Asn Glu Pro Arg Ser Ala Pro Ala Met Glu Pro Asp Gly Arg Gly
            20                  25                  30

Ala Trp Ala His Ser Arg Ala Ala Leu Asp Arg Leu Glu Lys Leu Leu
```

```
        35                  40                  45

Arg Cys Ser Arg Cys Thr Asn Ile Leu Arg Glu Pro Val Cys Leu Gly
    50                  55                  60

Gly Cys Glu His Ile Phe Cys Ser Asn Cys Val Ser Asp Cys Ile Gly
65                  70                  75                  80

Thr Gly Cys Pro Val Cys Tyr Thr Pro Ala Trp Ile Gln Asp Leu Lys
                85                  90                  95

Ile Asn Arg Gln Leu Asp Ser Met Ile Gln Leu Cys Ser Lys Leu Arg
            100                 105                 110

Asn Leu Leu His Asp Asn Glu Leu Ser Asp Leu Lys Glu Asp Lys Pro
        115                 120                 125

Arg Lys Ser Leu Phe Asn Asp Ala Gly Asn Lys Lys Asn Ser Ile Lys
    130                 135                 140

Met Trp Phe Ser Pro Arg Ser Lys Lys Val Arg Tyr Val Val Ser Lys
145                 150                 155                 160

Ala Ser Val Gln Thr Gln Pro Ala Ile Lys Lys Asp Ala Ser Ala Gln
                165                 170                 175

Gln Asp Ser Tyr Glu Phe Val Ser Pro Ser Pro Pro Ala Asp Val Ser
            180                 185                 190

Glu Arg Ala Lys Lys Ala Ser Ala Arg Ser Gly Lys Lys Gln Lys Lys
        195                 200                 205

Lys Thr Leu Ala Glu Ile Asn Gln Lys Trp Asn Leu Glu Ala Glu Lys
    210                 215                 220

Glu Asp Gly Glu Phe Asp Ser Lys Glu Glu Ser Lys Gln Lys Leu Val
225                 230                 235                 240

Ser Phe Cys Ser Gln Pro Ser Val Ile Ser Ser Pro Gln Ile Asn Gly
                245                 250                 255

Glu Ile Asp Leu Leu Ala Ser Gly Ser Leu Thr Glu Ser Glu Cys Phe
            260                 265                 270

Gly Ser Leu Thr Glu Val Ser Leu Pro Leu Ala Glu Gln Ile Glu Ser
        275                 280                 285

Pro Asp Thr Lys Ser Arg Asn Glu Val Val Thr Pro Glu Lys Val Cys
    290                 295                 300

Lys Asn Tyr Leu Thr Ser Lys Lys Ser Leu Pro Leu Glu Asn Asn Gly
305                 310                 315                 320

Lys Arg Gly His His Asn Arg Leu Ser Ser Pro Ile Ser Lys Arg Cys
                325                 330                 335

Arg Thr Ser Ile Leu Ser Thr Ser Gly Asp Phe Val Lys Gln Thr Val
            340                 345                 350

Pro Ser Glu Asn Ile Pro Leu Pro Glu Cys Ser Ser Pro Pro Ser Cys
```

```
        355                 360                 365

Lys Arg Lys Val Gly Gly Thr Ser Gly Arg Lys Asn Ser Asn Met Ser
    370                 375                 380

Asp Glu Phe Ile Ser Leu Ser Pro Gly Thr Pro Pro Ser Thr Leu Ser
385                 390                 395                 400

Ser Ser Ser Tyr Arg Gln Val Met Ser Ser Pro Ser Ala Met Lys Leu
                405                 410                 415

Leu Pro Asn Met Ala Val Lys Arg Asn His Arg Gly Glu Thr Leu Leu
            420                 425                 430

His Ile Ala Ser Ile Lys Gly Asp Ile Pro Ser Val Glu Tyr Leu Leu
        435                 440                 445

Gln Asn Gly Ser Asp Pro Asn Val Lys Asp His Ala Gly Trp Thr Pro
    450                 455                 460

Leu His Glu Ala Cys Asn His Gly His Leu Lys Val Val Glu Leu Leu
465                 470                 475                 480

Leu Gln His Lys Ala Leu Val Asn Thr Thr Gly Tyr Gln Asn Asp Ser
                485                 490                 495

Pro Leu His Asp Ala Ala Lys Asn Gly His Val Asp Ile Val Lys Leu
            500                 505                 510

Leu Leu Ser Tyr Gly Ala Ser Arg Asn Ala Val Asn Ile Phe Gly Leu
        515                 520                 525

Arg Pro Val Asp Tyr Thr Asp Asp Glu Ser Met Lys Ser Leu Leu Leu
    530                 535                 540

Leu Pro Glu Lys Asn Glu Ser Ser Ser Ala Ser His Cys Ser Val Met
545                 550                 555                 560

Asn Thr Gly Gln Arg Arg Asp Gly Pro Leu Val Leu Ile Gly Ser Gly
                565                 570                 575

Leu Ser Ser Glu Gln Gln Lys Met Leu Ser Glu Leu Ala Val Ile Leu
            580                 585                 590

Lys Ala Lys Lys Tyr Thr Glu Phe Asp Ser Thr Val Thr His Val Val
        595                 600                 605

Val Pro Gly Asp Ala Val Gln Ser Thr Leu Lys Cys Met Leu Gly Ile
    610                 615                 620

Leu Asn Gly Cys Trp Ile Leu Lys Phe Glu Trp Val Lys Ala Cys Leu
625                 630                 635                 640

Arg Arg Lys Val Cys Glu Gln Glu Glu Lys Tyr Glu Ile Pro Glu Gly
                645                 650                 655

Pro Arg Arg Ser Arg Leu Asn Arg Glu Gln Leu Leu Pro Lys Leu Phe
            660                 665                 670

Asp Gly Cys Tyr Phe Tyr Leu Trp Gly Thr Phe Lys His His Pro Lys
```

675 680 685

Asp Asn Leu Ile Lys Leu Val Thr Ala Gly Gly Gly Gln Ile Leu Ser
690 695 700

Arg Lys Pro Lys Pro Asp Ser Asp Val Thr Gln Thr Ile Asn Thr Val
705 710 715 720

Ala Tyr His Ala Arg Pro Asp Ser Asp Gln Arg Phe Cys Thr Gln Tyr
725 730 735

Ile Ile Tyr Glu Asp Leu Cys Asn Tyr His Pro Glu Arg Val Arg Gln
740 745 750

Gly Lys Val Trp Lys Ala Pro Ser Ser Trp Phe Ile Asp Cys Val Met
755 760 765

Ser Phe Glu Leu Leu Pro Leu Asp Ser
770 775

<210> 58
<211> 323
<212> PRT
<213> Homo Sapiens

<400> 58

Met Tyr His Asn Ser Ser Gln Lys Arg His Trp Thr Phe Ser Ser Glu
1 5 10 15

Glu Gln Leu Ala Arg Leu Arg Ala Asp Ala Asn Arg Lys Phe Arg Cys
20 25 30

Lys Ala Val Ala Asn Gly Lys Val Leu Pro Asn Asp Pro Val Phe Leu
35 40 45

Glu Pro His Glu Glu Met Thr Leu Cys Lys Tyr Tyr Glu Lys Arg Leu
50 55 60

Leu Glu Phe Cys Ser Val Phe Lys Pro Ala Met Pro Arg Ser Val Val
65 70 75 80

Gly Thr Ala Cys Met Tyr Phe Lys Arg Phe Tyr Leu Asn Asn Ser Val
85 90 95

Met Glu Tyr His Pro Arg Ile Ile Met Leu Thr Cys Ala Phe Leu Ala
100 105 110

Cys Lys Val Asp Glu Phe Asn Val Ser Ser Pro Gln Phe Val Gly Asn
115 120 125

Leu Arg Glu Ser Pro Leu Gly Gln Glu Lys Ala Leu Glu Gln Ile Leu
130 135 140

Glu Tyr Glu Leu Leu Leu Ile Gln Gln Leu Asn Phe His Leu Ile Val
145 150 155 160

His Asn Pro Tyr Arg Pro Phe Glu Gly Phe Leu Ile Asp Leu Lys Thr
165 170 175

```
Arg Tyr Pro Ile Leu Glu Asn Pro Glu Ile Leu Arg Lys Thr Ala Asp
            180                 185                 190

Asp Phe Leu Asn Arg Ile Ala Leu Thr Asp Ala Tyr Leu Leu Tyr Thr
        195                 200                 205

Pro Ser Gln Ile Ala Leu Thr Ala Ile Leu Ser Ser Ala Ser Arg Ala
    210                 215                 220

Gly Ile Thr Met Glu Ser Tyr Leu Ser Glu Ser Leu Met Leu Lys Glu
225                 230                 235                 240

Asn Arg Thr Cys Leu Ser Gln Leu Leu Asp Ile Met Lys Ser Met Arg
                245                 250                 255

Asn Leu Val Lys Lys Tyr Glu Pro Pro Arg Ser Glu Glu Val Ala Val
            260                 265                 270

Leu Lys Gln Lys Leu Glu Arg Cys His Ser Ala Glu Leu Ala Leu Asn
        275                 280                 285

Val Ile Thr Lys Lys Arg Lys Gly Tyr Glu Asp Asp Asp Tyr Val Ser
    290                 295                 300

Lys Lys Ser Lys His Glu Glu Glu Glu Trp Thr Asp Asp Asp Leu Val
305                 310                 315                 320

Glu Ser Leu
```

<210> 59
<211> 217
<212> PRT
<213> Homo Sapiens

<400> 59

```
Met Ala Ser Leu Ser Leu Ala Pro Val Asn Ile Phe Lys Ala Gly Ala
1               5                   10                  15

Asp Glu Glu Arg Ala Glu Thr Ala Arg Leu Thr Ser Phe Ile Gly Ala
            20                  25                  30

Ile Ala Ile Gly Asp Leu Val Lys Ser Thr Leu Gly Pro Lys Gly Met
        35                  40                  45

Asp Lys Ile Leu Leu Ser Ser Gly Arg Asp Ala Ser Leu Met Val Thr
    50                  55                  60

Asn Asp Gly Ala Thr Ile Leu Lys Asn Ile Gly Val Asp Asn Pro Ala
65                  70                  75                  80

Ala Lys Val Leu Val Asp Met Ser Arg Val Gln Asp Asp Glu Val Gly
                85                  90                  95

Asp Gly Thr Thr Ser Val Thr Val Leu Ala Ala Glu Leu Leu Arg Glu
            100                 105                 110

Ala Glu Ser Leu Ile Ala Lys Lys Ile His Pro Gln Thr Ile Ile Ala
        115                 120                 125
```

```
Gly Trp Arg Glu Ala Thr Lys Ala Ala Arg Glu Ala Leu Leu Ser Ser
    130                 135                 140

Ala Val Asp His Gly Ser Asp Glu Val Lys Phe Arg Gln Asp Leu Met
145                 150                 155                 160

Asn Ile Ala Gly Thr Thr Leu Ser Ser Lys Leu Leu Thr His His Lys
                165                 170                 175

Asp His Phe Thr Lys Leu Ala Val Glu Ala Val Leu Arg Leu Lys Gly
            180                 185                 190

Ser Gly Asn Leu Glu Ala Ile His Ile Ile Lys Lys Leu Gly Gly Ser
        195                 200                 205

Leu Ala Asp Ser Tyr Leu Asp Glu Gly
    210                 215
```

<210> 60
<211> 499
<212> PRT
<213> Homo Sapiens

<400> 60

```
Met Ala Gln Phe Ala Phe Glu Ser Asp Leu His Ser Leu Leu Gln Leu
1               5                   10                  15

Asp Ala Pro Ile Pro Asn Ala Pro Pro Ala Arg Trp Gln Arg Lys Ala
            20                  25                  30

Lys Glu Ala Ala Gly Pro Ala Pro Ser Pro Met Arg Ala Ala Asn Arg
        35                  40                  45

Ser His Ser Ala Gly Arg Thr Pro Gly Arg Thr Pro Gly Lys Ser Ser
    50                  55                  60

Ser Lys Val Gln Thr Thr Pro Ser Lys Pro Gly Gly Asp Arg Tyr Ile
65                  70                  75                  80

Pro His Arg Ser Ala Ala Gln Met Glu Val Ala Ser Phe Leu Leu Ser
                85                  90                  95

Lys Glu Asn Gln Ser Glu Asn Ser Gln Thr Pro Thr Lys Lys Glu His
            100                 105                 110

Gln Lys Ala Trp Ala Leu Asn Leu Asn Gly Phe Asp Val Glu Glu Ala
        115                 120                 125

Lys Ile Leu Arg Leu Ser Gly Lys Pro Gln Asn Ala Pro Glu Gly Tyr
    130                 135                 140

Gln Asn Arg Leu Lys Val Leu Tyr Ser Gln Lys Ala Thr Pro Gly Ser
145                 150                 155                 160

Ser Arg Lys Thr Cys Arg Tyr Ile Pro Ser Leu Pro Asp Arg Ile Leu
                165                 170                 175

Asp Ala Pro Glu Ile Arg Asn Asp Tyr Tyr Leu Asn Leu Val Asp Trp
```

```
            180                 185                 190

Ser Ser Gly Asn Val Leu Ala Val Ala Leu Asp Asn Ser Val Tyr Leu
        195                 200                 205

Trp Ser Ala Ser Ser Gly Asp Ile Leu Gln Leu Leu Gln Met Glu Gln
    210                 215                 220

Pro Gly Glu Tyr Ile Ser Ser Val Ala Trp Ile Lys Glu Gly Asn Tyr
225                 230                 235                 240

Leu Ala Val Gly Thr Ser Ser Ala Glu Val Gln Leu Trp Asp Val Gln
                245                 250                 255

Gln Gln Lys Arg Leu Arg Asn Met Thr Ser His Ser Ala Arg Val Gly
            260                 265                 270

Ser Leu Ser Trp Asn Ser Tyr Ile Leu Ser Ser Gly Ser Arg Ser Gly
        275                 280                 285

His Ile His His His Asp Val Arg Val Ala Glu His His Val Ala Thr
    290                 295                 300

Leu Ser Gly His Ser Gln Glu Val Cys Gly Leu Arg Trp Ala Pro Asp
305                 310                 315                 320

Gly Arg His Leu Ala Ser Gly Gly Asn Asp Asn Leu Val Asn Val Trp
                325                 330                 335

Pro Ser Ala Pro Gly Glu Gly Gly Trp Val Pro Leu Gln Thr Phe Thr
            340                 345                 350

Gln His Gln Gly Ala Val Lys Ala Val Ala Trp Cys Pro Trp Gln Ser
        355                 360                 365

Asn Val Leu Ala Thr Gly Gly Gly Thr Ser Asp Arg His Ile Arg Ile
    370                 375                 380

Trp Asn Val Cys Ser Gly Ala Cys Leu Ser Ala Val Asp Ala His Ser
385                 390                 395                 400

Gln Val Cys Ser Ile Leu Trp Ser Pro His Tyr Lys Glu Leu Ile Ser
                405                 410                 415

Gly His Gly Phe Ala Gln Asn Gln Leu Val Ile Trp Lys Tyr Pro Thr
            420                 425                 430

Met Ala Lys Val Ala Glu Leu Lys Gly His Thr Ser Arg Val Leu Ser
        435                 440                 445

Leu Thr Met Ser Pro Asp Gly Ala Thr Val Ala Ser Ala Ala Ala Asp
    450                 455                 460

Glu Thr Leu Arg Leu Trp Arg Cys Phe Glu Leu Asp Pro Ala Arg Arg
465                 470                 475                 480

Arg Glu Arg Glu Lys Ala Ser Ala Ala Lys Ser Ser Leu Ile His Gln
                485                 490                 495

Gly Ile Arg
```

<210> 61
<211> 298
<212> PRT
<213> Homo Sapiens

<400> 61

Ile Ala Ala Ala Pro Glu Leu Leu Glu Arg Ser Gly Ser Pro Gly Gly
1 5 10 15

Gly Gly Gly Ala Glu Glu Glu Ala Gly Gly Gly Pro Gly Gly Ser Pro
20 25 30

Pro Asp Gly Ala Arg Pro Gly Pro Ser Arg Glu Leu Ala Val Val Ala
35 40 45

Arg Pro Arg Ala Ala Pro Thr Pro Gly Pro Ser Ala Ala Ala Met Ala
50 55 60

Arg Pro Leu Val Pro Ser Ser Gln Lys Ala Leu Leu Leu Glu Leu Lys
65 70 75 80

Gly Leu Gln Glu Glu Pro Val Glu Gly Phe Arg Val Thr Leu Val Asp
85 90 95

Glu Gly Asp Leu Tyr Asn Trp Glu Val Ala Ile Phe Gly Pro Pro Asn
100 105 110

Thr Tyr Tyr Glu Gly Gly Tyr Phe Lys Ala Arg Leu Lys Phe Pro Ile
115 120 125

Asp Tyr Pro Tyr Ser Pro Pro Ala Phe Arg Phe Leu Thr Lys Met Trp
130 135 140

His Pro Asn Ile Tyr Glu Thr Gly Asp Val Cys Ile Ser Ile Leu His
145 150 155 160

Pro Pro Val Asp Asp Pro Gln Ser Gly Glu Leu Pro Ser Glu Arg Trp
165 170 175

Asn Pro Thr Gln Asn Val Arg Thr Ile Leu Leu Ser Val Ile Ser Leu
180 185 190

Leu Asn Glu Pro Asn Thr Phe Ser Pro Ala Asn Val Asp Ala Ser Val
195 200 205

Met Tyr Arg Lys Trp Lys Glu Ser Lys Gly Lys Asp Arg Glu Tyr Thr
210 215 220

Asp Ile Ile Arg Lys Gln Val Leu Gly Thr Lys Val Asp Ala Glu Arg
225 230 235 240

Asp Gly Val Lys Val Pro Thr Thr Leu Ala Glu Tyr Cys Val Lys Thr
245 250 255

Lys Ala Pro Ala Pro Asp Glu Gly Ser Asp Leu Phe Tyr Asp Asp Tyr
260 265 270

Tyr Glu Asp Gly Glu Val Glu Glu Glu Ala Asp Ser Cys Phe Gly Asp
275 280 285

Asp Glu Asp Asp Ser Gly Thr Glu Glu Ser
290 295

<210> 62
<211> 212
<212> PRT
<213> Homo Sapiens

<400> 62

Met Glu Pro Pro Ser Ser Ile Gln Thr Ser Glu Phe Asp Ser Ser Asp
1 5 10 15

Glu Glu Pro Ile Glu Asp Glu Gln Thr Pro Ile His Ile Ser Trp Leu
20 25 30

Ser Leu Ser Arg Val Asn Cys Ser Gln Phe Leu Gly Leu Cys Ala Leu
35 40 45

Pro Gly Cys Lys Phe Lys Asp Val Arg Arg Asn Val Gln Lys Asp Thr
50 55 60

Glu Glu Leu Lys Ser Cys Gly Ile Gln Asp Ile Phe Val Phe Cys Thr
65 70 75 80

Arg Gly Glu Leu Ser Lys Tyr Arg Val Pro Asn Leu Leu Asp Leu Tyr
85 90 95

Gln Gln Cys Gly Ile Ile Thr His His His Pro Ile Ala Asp Gly Gly
100 105 110

Thr Pro Asp Ile Ala Ser Cys Cys Glu Ile Met Glu Glu Leu Thr Thr
115 120 125

Cys Leu Lys Asn Tyr Arg Lys Thr Leu Ile His Cys Tyr Gly Gly Leu
130 135 140

Gly Arg Ser Cys Leu Val Ala Ala Cys Leu Leu Leu Tyr Leu Ser Asp
145 150 155 160

Thr Ile Ser Pro Glu Gln Ala Ile Asp Ser Leu Arg Asp Leu Arg Gly
165 170 175

Ser Gly Ala Ile Gln Thr Ile Lys Gln Tyr Asn Tyr Leu His Glu Phe
180 185 190

Arg Asp Lys Leu Ala Ala His Leu Ser Ser Arg Asp Ser Gln Ser Arg
195 200 205

Ser Val Ser Arg
210

<210> 63
<211> 79
<212> PRT
<213> Homo Sapiens

<400> 63

Met Ser His Lys Gln Ile Tyr Tyr Ser Asp Lys Tyr Asp Asp Glu Glu
1 5 10 15

Phe Glu Tyr Arg His Val Met Leu Pro Lys Asp Ile Ala Lys Leu Val
20 25 30

Pro Lys Thr His Leu Met Ser Glu Ser Glu Trp Arg Asn Leu Gly Val
35 40 45

Gln Gln Ser Gln Gly Trp Val His Tyr Met Ile His Glu Pro Glu Pro
50 55 60

His Ile Leu Leu Phe Arg Arg Pro Leu Pro Lys Lys Pro Lys Lys
65 70 75

<210> 64
<211> 79
<212> PRT
<213> Homo Sapiens

<400> 64

Met Ala His Lys Gln Ile Tyr Tyr Ser Asp Lys Tyr Phe Asp Glu His
1 5 10 15

Tyr Glu Tyr Arg His Val Met Leu Pro Arg Glu Leu Ser Lys Gln Val
20 25 30

Pro Lys Thr His Leu Met Ser Glu Glu Glu Trp Arg Arg Leu Gly Val
35 40 45

Gln Gln Ser Leu Gly Trp Val His Tyr Met Ile His Glu Pro Glu Pro
50 55 60

His Ile Leu Leu Phe Arg Arg Pro Leu Pro Lys Asp Gln Gln Lys
65 70 75

<210> 65
<211> 79
<212> PRT
<213> Homo Sapiens

<400> 65

Met Gln Ala Leu Arg Val Ser Gln Ala Leu Ile Arg Ser Phe Ser Ser
1 5 10 15

Thr Ala Arg Asn Arg Phe Gln Asn Arg Val Arg Glu Lys Gln Lys Leu
20 25 30

Phe Gln Glu Asp Asn Asp Ile Pro Leu Tyr Leu Lys Gly Gly Ile Val
35 40 45

Asp Asn Ile Leu Tyr Arg Val Thr Met Thr Leu Cys Leu Gly Gly Thr
50 55 60

Val Tyr Ser Leu Tyr Ser Leu Gly Trp Ala Ser Phe Pro Arg Asn
65 70 75

<210> 66
<211> 417
<212> PRT
<213> Homo Sapiens

<400> 66

Met Arg Leu Ile Leu Pro Val Gly Leu Ile Ala Thr Thr Leu Ala Ile
1 5 10 15

Ala Pro Val Arg Phe Asp Arg Glu Lys Val Phe Arg Val Lys Pro Gln
20 25 30

Asp Glu Lys Gln Ala Asp Ile Ile Lys Asp Leu Ala Lys Thr Asn Glu
35 40 45

Leu Asp Phe Trp Tyr Pro Gly Ala Thr His His Val Ala Ala Asn Met
50 55 60

Met Val Asp Phe Arg Val Ser Glu Lys Glu Ser Gln Ala Ile Gln Ser
65 70 75 80

Ala Leu Asp Gln Asn Lys Met His Tyr Glu Ile Leu Ile His Asp Leu
85 90 95

Gln Glu Glu Ile Glu Lys Gln Phe Asp Val Lys Glu Asp Ile Pro Gly
100 105 110

Arg His Ser Tyr Ala Lys Tyr Asn Asn Trp Glu Lys Ile Val Ala Trp
115 120 125

Thr Glu Lys Met Met Asp Lys Tyr Pro Glu Met Val Ser Arg Ile Lys
130 135 140

Ile Gly Ser Thr Val Glu Asp Asn Pro Leu Tyr Val Leu Lys Ile Gly
145 150 155 160

Glu Lys Asn Glu Arg Arg Lys Ala Ile Phe Met Asp Cys Gly Ile His
165 170 175

Ala Arg Glu Trp Val Ser Pro Ala Phe Cys Gln Trp Phe Val Tyr Gln
180 185 190

Ala Thr Lys Thr Tyr Gly Arg Asn Lys Ile Met Thr Lys Leu Leu Asp
195 200 205

Arg Met Asn Phe Tyr Ile Leu Pro Val Phe Asn Val Asp Gly Tyr Ile
210 215 220

Trp Ser Trp Thr Lys Asn Arg Met Trp Arg Lys Asn Arg Ser Lys Asn
225 230 235 240

Gln Asn Ser Lys Cys Ile Gly Thr Asp Leu Asn Arg Asn Phe Asn Ala
245 250 255

Ser Trp Asn Ser Ile Pro Asn Thr Asn Asp Pro Cys Ala Asp Asn Tyr
260 265 270

Arg Gly Ser Ala Pro Glu Ser Glu Lys Glu Thr Lys Ala Val Thr Asn

275 280 285

Phe Ile Arg Ser His Leu Asn Glu Ile Lys Val Tyr Ile Thr Phe His
290 295 300

Ser Tyr Ser Gln Met Leu Leu Phe Pro Tyr Gly Tyr Thr Ser Lys Leu
305 310 315 320

Pro Pro Asn His Glu Asp Leu Ala Lys Val Ala Lys Ile Gly Thr Asp
325 330 335

Val Leu Ser Thr Arg Tyr Glu Thr Arg Tyr Ile Tyr Gly Pro Ile Glu
340 345 350

Ser Thr Ile Tyr Pro Ile Ser Gly Ser Ser Leu Asp Trp Ala Tyr Asp
355 360 365

Leu Gly Ile Lys His Thr Phe Ala Phe Glu Leu Arg Asp Lys Gly Lys
370 375 380

Phe Gly Phe Leu Leu Pro Glu Ser Arg Ile Lys Pro Thr Cys Arg Glu
385 390 395 400

Thr Met Leu Ala Val Lys Phe Ile Ala Lys Tyr Ile Leu Lys His Thr
405 410 415

Ser

<210> 67
<211> 476
<212> PRT
<213> Homo Sapiens

<400> 67

Met Ala Gly Arg Gly Gly Ser Ala Leu Leu Ala Leu Cys Gly Ala Leu
1 5 10 15

Ala Ala Cys Gly Trp Leu Leu Gly Ala Glu Ala Gln Glu Pro Gly Ala
20 25 30

Pro Ala Ala Gly Met Arg Arg Arg Arg Arg Leu Gln Gln Glu Asp Gly
35 40 45

Ile Ser Phe Glu Tyr His Arg Tyr Pro Glu Leu Arg Glu Ala Leu Val
50 55 60

Ser Val Trp Leu Gln Cys Thr Ala Ile Ser Arg Ile Tyr Thr Val Gly
65 70 75 80

Arg Ser Phe Glu Gly Arg Glu Leu Leu Val Ile Glu Leu Ser Asp Asn
85 90 95

Pro Gly Val His Glu Pro Gly Glu Pro Glu Phe Lys Tyr Ile Gly Asn
100 105 110

Met His Gly Asn Glu Ala Val Gly Arg Glu Leu Leu Ile Phe Leu Ala
115 120 125

```
Gln Tyr Leu Cys Asn Glu Tyr Gln Lys Gly Asn Glu Thr Ile Val Asn
    130                 135                 140

Leu Ile His Ser Thr Arg Ile His Ile Met Pro Ser Leu Asn Pro Asp
145                 150                 155                 160

Gly Phe Glu Lys Ala Ala Ser Gln Pro Gly Glu Leu Lys Asp Trp Phe
                165                 170                 175

Val Gly Arg Ser Asn Ala Gln Gly Ile Asp Leu Asn Arg Asn Phe Pro
            180                 185                 190

Asp Leu Asp Arg Ile Val Tyr Val Asn Glu Lys Glu Gly Gly Pro Asn
        195                 200                 205

Asn His Leu Leu Lys Asn Met Lys Lys Ile Val Asp Gln Asn Thr Lys
    210                 215                 220

Leu Ala Pro Glu Thr Lys Ala Val Ile His Trp Ile Met Asp Ile Pro
225                 230                 235                 240

Phe Val Leu Ser Ala Asn Leu His Gly Gly Asp Leu Val Ala Asn Tyr
                245                 250                 255

Pro Tyr Asp Glu Thr Arg Ser Gly Ser Ala His Glu Tyr Ser Ser Ser
            260                 265                 270

Pro Asp Asp Ala Ile Phe Gln Ser Leu Ala Arg Ala Tyr Ser Ser Phe
        275                 280                 285

Asn Pro Ala Met Ser Asp Pro Asn Arg Pro Pro Cys Arg Lys Asn Asp
    290                 295                 300

Asp Asp Ser Ser Phe Val Asp Gly Thr Thr Asn Gly Gly Ala Trp Tyr
305                 310                 315                 320

Ser Val Pro Gly Gly Met Gln Asp Phe Asn Tyr Leu Ser Ser Asn Cys
                325                 330                 335

Phe Glu Ile Thr Val Glu Leu Ser Cys Glu Lys Phe Pro Pro Glu Glu
            340                 345                 350

Thr Leu Lys Thr Tyr Trp Glu Asp Asn Lys Asn Ser Leu Ile Ser Tyr
        355                 360                 365

Leu Glu Gln Ile His Arg Gly Val Lys Gly Phe Val Arg Asp Leu Gln
    370                 375                 380

Gly Asn Pro Ile Ala Asn Ala Thr Ile Ser Val Glu Gly Ile Asp His
385                 390                 395                 400

Asp Val Thr Ser Ala Lys Asp Gly Asp Tyr Trp Arg Leu Leu Ile Pro
                405                 410                 415

Gly Asn Tyr Lys Leu Thr Ala Ser Ala Pro Gly Tyr Leu Ala Ile Thr
            420                 425                 430

Lys Lys Val Ala Val Pro Tyr Ser Pro Ala Ala Gly Val Asp Phe Glu
        435                 440                 445
```

```
Leu Glu Ser Phe Ser Glu Arg Lys Glu Glu Glu Lys Glu Glu Leu Met
    450                 455                 460

Glu Trp Trp Lys Met Met Ser Glu Thr Leu Asn Phe
465                 470                 475

<210>  68
<211>  355
<212>  PRT
<213>  Homo Sapiens

<400>  68

Met Asp Gln Phe Pro Glu Ser Val Thr Glu Asn Phe Glu Tyr Asp Asp
1               5                   10                  15

Leu Ala Glu Ala Cys Tyr Ile Gly Asp Ile Val Val Phe Gly Thr Val
            20                  25                  30

Phe Leu Ser Ile Phe Tyr Ser Val Ile Phe Ala Ile Gly Leu Val Gly
        35                  40                  45

Asn Leu Leu Val Val Phe Ala Leu Thr Asn Ser Lys Lys Pro Lys Ser
    50                  55                  60

Val Thr Asp Ile Tyr Leu Leu Asn Leu Ala Leu Ser Asp Leu Leu Phe
65                  70                  75                  80

Val Ala Thr Leu Pro Phe Trp Thr His Tyr Leu Ile Asn Glu Lys Gly
                85                  90                  95

Leu His Asn Ala Met Cys Lys Phe Thr Thr Ala Phe Phe Phe Ile Gly
            100                 105                 110

Phe Phe Gly Ser Ile Phe Phe Ile Thr Val Ile Ser Ile Asp Arg Tyr
        115                 120                 125

Leu Ala Ile Val Leu Ala Ala Asn Ser Met Asn Asn Arg Thr Val Gln
    130                 135                 140

His Gly Val Thr Ile Ser Leu Gly Val Trp Ala Ala Ala Ile Leu Val
145                 150                 155                 160

Ala Ala Pro Gln Phe Met Phe Thr Lys Gln Lys Glu Asn Glu Cys Leu
                165                 170                 175

Gly Asp Tyr Pro Glu Val Leu Gln Glu Ile Trp Pro Val Leu Arg Asn
            180                 185                 190

Val Glu Thr Asn Phe Leu Gly Phe Leu Leu Pro Leu Leu Ile Met Ser
        195                 200                 205

Tyr Cys Tyr Phe Arg Ile Ile Gln Thr Leu Phe Ser Cys Lys Asn His
    210                 215                 220

Lys Lys Ala Lys Ala Ile Lys Leu Ile Leu Leu Val Val Ile Val Phe
225                 230                 235                 240

Phe Leu Phe Trp Thr Pro Tyr Asn Val Met Ile Phe Leu Glu Thr Leu
                245                 250                 255
```

```
Lys Leu Tyr Asp Phe Phe Pro Ser Cys Asp Met Arg Lys Asp Leu Arg
            260                 265                 270

Leu Ala Leu Ser Val Thr Glu Thr Val Ala Phe Ser His Cys Cys Leu
        275                 280                 285

Asn Pro Leu Ile Tyr Ala Phe Ala Gly Glu Lys Phe Arg Arg Tyr Leu
    290                 295                 300

Tyr His Leu Tyr Gly Lys Cys Leu Ala Val Leu Cys Gly Arg Ser Val
305                 310                 315                 320

His Val Asp Phe Ser Ser Ser Glu Ser Gln Arg Ser Arg His Gly Ser
                325                 330                 335

Val Leu Ser Ser Asn Phe Thr Tyr His Thr Ser Asp Gly Asp Ala Leu
            340                 345                 350

Leu Leu Leu
        355
```

<210> 69
<211> 767
<212> PRT
<213> Homo Sapiens

<400> 69

```
Met Ser Gln Arg Pro Arg Ala Pro Arg Ser Ala Leu Trp Leu Leu Ala
1               5                   10                  15

Pro Pro Leu Leu Arg Trp Ala Pro Pro Leu Leu Thr Val Leu His Ser
            20                  25                  30

Asp Leu Phe Gln Ala Leu Leu Asp Ile Leu Asp Tyr Tyr Glu Ala Ser
        35                  40                  45

Leu Ser Glu Ser Gln Lys Tyr Arg Tyr Gln Asp Glu Asp Thr Pro Pro
    50                  55                  60

Leu Glu His Ser Pro Ala His Leu Pro Asn Gln Ala Asn Ser Pro Pro
65                  70                  75                  80

Val Ile Val Asn Thr Asp Thr Leu Glu Ala Pro Gly Tyr Glu Leu Gln
                85                  90                  95

Val Asn Gly Thr Glu Gly Glu Met Glu Tyr Glu Glu Ile Thr Leu Glu
            100                 105                 110

Arg Gly Asn Ser Gly Leu Gly Phe Ser Ile Ala Gly Gly Thr Asp Asn
        115                 120                 125

Pro His Ile Gly Asp Asp Pro Ser Ile Phe Ile Thr Lys Ile Ile Pro
    130                 135                 140

Gly Gly Ala Ala Ala Gln Asp Gly Arg Leu Arg Val Asn Asp Ser Ile
145                 150                 155                 160

Leu Phe Val Asn Glu Val Asp Val Arg Glu Val Thr His Ser Ala Ala
```

```
                165                 170                 175

Val Glu Ala Leu Lys Glu Ala Gly Ser Ile Val Arg Leu Tyr Val Met
            180                 185                 190

Arg Arg Lys Pro Pro Ala Glu Lys Val Met Glu Ile Lys Leu Ile Lys
        195                 200                 205

Gly Pro Lys Gly Leu Gly Phe Ser Ile Ala Gly Gly Val Gly Asn Gln
    210                 215                 220

His Ile Pro Gly Asp Asn Ser Ile Tyr Val Thr Lys Ile Ile Glu Gly
225                 230                 235                 240

Gly Ala Ala His Lys Asp Gly Arg Leu Gln Ile Gly Asp Lys Ile Leu
                245                 250                 255

Ala Val Asn Ser Val Gly Leu Glu Asp Val Met His Glu Asp Ala Val
            260                 265                 270

Ala Ala Leu Lys Asn Thr Tyr Asp Val Val Tyr Leu Lys Val Ala Lys
        275                 280                 285

Pro Ser Asn Ala Tyr Leu Ser Asp Ser Tyr Ala Pro Pro Asp Ile Thr
    290                 295                 300

Thr Ser Tyr Ser Gln His Leu Asp Asn Glu Ile Ser His Ser Ser Tyr
305                 310                 315                 320

Leu Gly Thr Asp Tyr Pro Thr Ala Met Thr Pro Thr Ser Pro Arg Arg
                325                 330                 335

Tyr Ser Pro Val Ala Lys Asp Leu Leu Gly Glu Glu Asp Ile Pro Arg
            340                 345                 350

Glu Pro Arg Arg Ile Val Ile His Arg Gly Ser Thr Gly Leu Gly Phe
        355                 360                 365

Asn Ile Val Gly Gly Glu Asp Gly Glu Gly Ile Phe Ile Ser Phe Ile
    370                 375                 380

Leu Ala Gly Gly Pro Ala Asp Leu Ser Gly Glu Leu Arg Lys Gly Asp
385                 390                 395                 400

Gln Ile Leu Ser Val Asn Gly Val Asp Leu Arg Asn Ala Ser His Glu
                405                 410                 415

Gln Ala Ala Ile Ala Leu Lys Asn Ala Gly Gln Thr Val Thr Ile Ile
            420                 425                 430

Ala Gln Tyr Lys Pro Glu Glu Tyr Ser Arg Phe Glu Ala Lys Ile His
        435                 440                 445

Asp Leu Arg Glu Gln Leu Met Asn Ser Ser Leu Gly Ser Gly Thr Ala
    450                 455                 460

Ser Leu Arg Ser Asn Pro Lys Arg Gly Phe Tyr Ile Arg Ala Leu Phe
465                 470                 475                 480

Asp Tyr Asp Lys Thr Lys Asp Cys Gly Phe Leu Ser Gln Ala Leu Ser
```

```
                485                 490                 495

Phe Arg Phe Gly Asp Val Leu His Val Ile Asp Ala Ser Asp Glu Glu
            500                 505                 510

Trp Trp Gln Ala Arg Arg Val His Ser Asp Ser Glu Thr Asp Asp Ile
        515                 520                 525

Gly Phe Ile Pro Ser Lys Arg Arg Val Glu Arg Arg Glu Trp Ser Arg
    530                 535                 540

Leu Lys Ala Lys Asp Trp Gly Ser Ser Ser Gly Ser Gln Gly Arg Glu
545                 550                 555                 560

Asp Ser Val Leu Ser Tyr Glu Thr Val Thr Gln Met Glu Val His Tyr
                565                 570                 575

Ala Arg Pro Ile Ile Ile Leu Gly Pro Thr Lys Asp Arg Ala Asn Asp
            580                 585                 590

Asp Leu Leu Ser Glu Phe Pro Asp Lys Phe Gly Ser Cys Val Pro His
        595                 600                 605

Thr Thr Arg Pro Lys Arg Glu Tyr Glu Ile Asp Gly Arg Asp Tyr His
    610                 615                 620

Phe Val Ser Ser Arg Glu Lys Met Glu Lys Asp Ile Gln Ala His Lys
625                 630                 635                 640

Phe Ile Glu Ala Gly Gln Tyr Asn Ser His Leu Tyr Gly Thr Ser Val
                645                 650                 655

Gln Ser Val Arg Glu Val Ala Glu Gln Gly Lys His Cys Ile Leu Asp
            660                 665                 670

Val Ser Ala Asn Ala Val Arg Arg Leu Gln Ala Ala His Leu His Pro
        675                 680                 685

Ile Ala Ile Phe Ile Arg Pro Arg Ser Leu Glu Asn Val Leu Glu Ile
    690                 695                 700

Asn Lys Arg Ile Thr Glu Glu Gln Ala Arg Lys Ala Phe Asp Arg Ala
705                 710                 715                 720

Thr Lys Leu Glu Gln Glu Phe Thr Glu Cys Phe Ser Ala Ile Val Glu
                725                 730                 735

Gly Asp Ser Phe Glu Glu Ile Tyr His Lys Val Lys Arg Val Ile Glu
            740                 745                 750

Asp Leu Ser Gly Pro Tyr Ile Trp Val Pro Ala Arg Glu Arg Leu
        755                 760                 765
```

<210> 70
<211> 752
<212> PRT
<213> Homo Sapiens

<400> 70

```
Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln
1               5                  10                  15

Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr
            20                  25                  30

Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala
        35                  40                  45

Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln
    50                  55                  60

Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn
65                  70                  75                  80

Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu
                85                  90                  95

Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu Leu Gln
            100                 105                 110

Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala Gly Ile
        115                 120                 125

Met Ala Glu Val Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp
    130                 135                 140

Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys
145                 150                 155                 160

Leu Glu Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu
                165                 170                 175

Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys
            180                 185                 190

Asn Leu Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu
        195                 200                 205

Glu Ser Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg
    210                 215                 220

Leu Glu Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys
225                 230                 235                 240

Thr Leu Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys
                245                 250                 255

Leu Lys Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln
            260                 265                 270

Val Glu Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu
        275                 280                 285

Thr Lys Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr
    290                 295                 300

Ser Val Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu
305                 310                 315                 320
```

Glu Glu Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn
325 330 335

Arg Leu Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys
340 345 350

Leu Asn Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn
355 360 365

Asn Lys Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys
370 375 380

Leu Lys Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp
385 390 395 400

Glu Tyr Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala
405 410 415

Gln Phe Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys
420 425 430

Tyr Lys Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe
435 440 445

Lys Arg Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu
450 455 460

Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp
465 470 475 480

Leu Ile Cys His Leu Gln Gly Asp His Ser Val Cys Lys Lys Lys Leu
485 490 495

Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn
500 505 510

Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg
515 520 525

Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys
530 535 540

Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser
545 550 555 560

Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu
565 570 575

Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser
580 585 590

Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp
595 600 605

Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met
610 615 620

Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu
625 630 635 640

```
Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His
                645                 650                 655

Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser
            660                 665                 670

Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro
        675                 680                 685

Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys
    690                 695                 700

Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser
705                 710                 715                 720

Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys
                725                 730                 735

Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Leu Phe Arg Phe Trp Leu
            740                 745                 750
```

<210> 71
<211> 105
<212> PRT
<213> Homo Sapiens

<400> 71

```
Met Gln Thr Gln Ala Glu Ala Leu Thr Ala Gly Met Ala Gly Val Ala
1               5                   10                  15

Thr Ala Ala Ala Gly Ala Trp Thr Gln Pro Gln Leu Arg Pro Val Glu
            20                  25                  30

Leu Pro Gln Arg Thr Arg Gln Val Arg Ala Glu Thr Pro Arg Leu Pro
        35                  40                  45

Gln Gly Val Thr Asn Ala Ala Ala His Ile His Pro Gln Arg Ala Phe
    50                  55                  60

Pro Asp Pro Leu Gly Gly Gly Asn Arg Pro Trp Val Pro Gly Thr Arg
65                  70                  75                  80

Cys Arg Ala Pro Pro Lys Gly Gly Trp Glu Gly Ser His Ser Glu Trp
                85                  90                  95

Gln Asp Pro Gly Arg Pro Leu Glu Ser
            100                 105
```

<210> 72
<211> 225
<212> PRT
<213> Homo Sapiens

<400> 72

```
Met Asn Ser Asn Val Glu Asn Leu Pro Pro His Ile Ile Arg Leu Val
1               5                   10                  15

Tyr Lys Glu Val Thr Thr Leu Thr Ala Asp Pro Pro Asp Gly Ile Lys
```

20 25 30

Val Phe Pro Asn Glu Glu Asp Leu Thr Asp Leu Gln Val Thr Ile Glu
35 40 45

Gly Pro Glu Gly Thr Pro Tyr Ala Gly Gly Leu Phe Arg Met Lys Leu
50 55 60

Leu Leu Gly Lys Asp Phe Pro Ala Ser Pro Pro Lys Gly Tyr Phe Leu
65 70 75 80

Thr Lys Ile Phe His Pro Asn Val Gly Ala Asn Gly Glu Ile Cys Val
85 90 95

Asn Val Leu Lys Arg Asp Trp Thr Ala Glu Leu Gly Ile Arg His Val
100 105 110

Leu Leu Thr Ile Lys Cys Leu Leu Ile His Pro Asn Pro Glu Ser Ala
115 120 125

Leu Asn Glu Glu Ala Gly Arg Leu Leu Leu Glu Asn Tyr Glu Glu Tyr
130 135 140

Ala Ala Arg Ala Arg Leu Leu Thr Glu Ile His Gly Gly Ala Gly Gly
145 150 155 160

Pro Ser Gly Arg Ala Glu Ala Gly Arg Ala Leu Ala Ser Gly Thr Glu
165 170 175

Ala Ser Ser Thr Asp Pro Gly Ala Pro Gly Gly Pro Gly Gly Ala Glu
180 185 190

Gly Pro Met Ala Lys Lys His Ala Gly Glu Arg Asp Lys Lys Leu Ala
195 200 205

Ala Lys Lys Lys Thr Asp Lys Lys Arg Ala Leu Arg Ala Leu Arg Arg
210 215 220

Leu
225

<210> 73
<211> 208
<212> PRT
<213> Homo Sapiens

<400> 73

Pro His Pro Met Pro Leu Arg Leu Pro Thr Pro Gly Gly Asn Gly Gln
1 5 10 15

Ala Gly Arg Pro Cys Arg Ser Thr Gly Gln Gly Asn Lys Arg Gly Ala
20 25 30

Ala Lys Cys Pro Asp Gln Glu Ala Pro Tyr Phe Arg Gly Lys Gly His
35 40 45

Val Val Leu Ala Pro His Pro Ile Pro Ser His Leu Gly Ala Pro Pro
50 55 60

```
Pro His Ser Leu His Leu Gln Gly Asn Leu Val Leu His Ala Gly Ala
65                  70                  75                  80

Leu Ile Phe Leu Gly Gly Gly Arg Arg Glu Gly Trp Pro Leu Gly Glu
                85                  90                  95

Pro Pro Thr Trp Gly Ser Ser Lys Asp Gly Ala Asp Thr Ser Trp Ala
            100                 105                 110

Val Pro Ala Pro Pro Ala His Gln Asp Pro Pro Leu Ala Ala Ile Gln
        115                 120                 125

Leu Val Pro Lys His Leu Lys Pro Gln Ser Trp Ile Arg Ser Ser Ile
    130                 135                 140

Pro Pro Leu Leu Gly Pro Leu Gly Arg Leu Leu Pro Thr Asp Arg Cys
145                 150                 155                 160

Ser Pro His Leu Gly Arg Phe Trp Val Gly Lys Pro Pro His Thr Gly
                165                 170                 175

Asn Ser His Leu Ala Pro Cys Arg Ile His Pro Arg Ile Arg Pro Phe
            180                 185                 190

Ile His Arg Ser Val His Pro Cys Pro Gln Leu Thr Ala Arg His His
        195                 200                 205
```

<210> 74
<211> 109
<212> PRT
<213> Homo Sapiens

<400> 74

```
Met Ala Tyr Gln Leu Tyr Arg Asn Thr Thr Leu Gly Asn Ser Leu Gln
1               5                   10                  15

Glu Ser Leu Asp Glu Leu Ile Gln Ser Gln Gln Ile Thr Pro Gln Leu
            20                  25                  30

Ala Leu Gln Val Leu Leu Gln Phe Asp Lys Ala Ile Asn Ala Ala Leu
        35                  40                  45

Ala Gln Arg Val Arg Asn Arg Val Asn Phe Arg Gly Ser Leu Asn Thr
    50                  55                  60

Tyr Arg Phe Cys Asp Asn Val Trp Thr Phe Val Leu Asn Asp Val Glu
65                  70                  75                  80

Phe Arg Glu Val Thr Glu Leu Ile Lys Val Asp Lys Val Lys Ile Val
                85                  90                  95

Ala Cys Asp Gly Lys Asn Thr Gly Ser Asn Thr Thr Glu
            100                 105
```

<210> 75
<211> 693
<212> PRT
<213> Homo Sapiens

<400> 75

```
Met Ala Leu Cys Asn Gly Asp Ser Lys Leu Glu Asn Ala Gly Gly Asp
1               5                  10                  15

Leu Lys Asp Gly His His His Tyr Glu Gly Ala Val Val Ile Leu Asp
            20                  25                  30

Ala Gly Ala Gln Tyr Gly Lys Val Ile Asp Arg Arg Val Arg Glu Leu
        35                  40                  45

Phe Val Gln Ser Glu Ile Phe Pro Leu Glu Thr Pro Ala Phe Ala Ile
    50                  55                  60

Lys Glu Gln Gly Phe Arg Ala Ile Ile Ile Ser Gly Gly Pro Asn Ser
65                  70                  75                  80

Val Tyr Ala Glu Asp Ala Pro Trp Phe Asp Pro Ala Ile Phe Thr Ile
                85                  90                  95

Gly Lys Pro Val Leu Gly Ile Cys Tyr Gly Met Gln Met Met Asn Lys
            100                 105                 110

Val Phe Gly Gly Thr Val His Lys Lys Ser Val Arg Glu Asp Gly Val
        115                 120                 125

Phe Asn Ile Ser Val Asp Asn Thr Cys Ser Leu Phe Arg Gly Leu Gln
    130                 135                 140

Lys Glu Glu Val Val Leu Leu Thr His Gly Asp Ser Val Asp Lys Val
145                 150                 155                 160

Ala Asp Gly Phe Lys Val Val Ala Arg Ser Gly Asn Ile Val Ala Gly
                165                 170                 175

Ile Ala Asn Glu Ser Lys Lys Leu Tyr Gly Ala Gln Phe His Pro Glu
            180                 185                 190

Val Gly Leu Thr Glu Asn Gly Lys Val Ile Leu Lys Asn Phe Leu Tyr
        195                 200                 205

Asp Ile Ala Gly Cys Ser Gly Thr Phe Thr Val Gln Asn Arg Glu Leu
    210                 215                 220

Glu Cys Ile Arg Glu Ile Lys Glu Arg Val Gly Thr Ser Lys Val Leu
225                 230                 235                 240

Val Leu Leu Ser Gly Gly Val Asp Ser Thr Val Cys Thr Ala Leu Leu
                245                 250                 255

Asn Arg Ala Leu Asn Gln Glu Gln Val Ile Ala Val His Ile Asp Asn
            260                 265                 270

Gly Phe Met Arg Lys Arg Glu Ser Gln Ser Val Glu Glu Ala Leu Lys
        275                 280                 285

Lys Leu Gly Ile Gln Val Lys Val Ile Asn Ala Ala His Ser Phe Tyr
    290                 295                 300

Asn Gly Thr Thr Thr Leu Pro Ile Ser Asp Glu Asp Arg Thr Pro Arg
```

```
305                 310                 315                 320

Lys Arg Ile Ser Lys Thr Leu Asn Met Thr Thr Ser Pro Glu Glu Lys
                325                 330                 335

Arg Lys Ile Ile Gly Asp Thr Phe Val Lys Ile Ala Asn Glu Val Ile
            340                 345                 350

Gly Glu Met Asn Leu Lys Pro Glu Glu Val Phe Leu Ala Gln Gly Thr
        355                 360                 365

Leu Arg Pro Asp Leu Ile Glu Ser Ala Ser Leu Val Ala Ser Gly Lys
    370                 375                 380

Ala Glu Leu Ile Lys Thr His His Asn Asp Thr Glu Leu Ile Arg Lys
385                 390                 395                 400

Leu Arg Glu Glu Gly Lys Val Ile Glu Pro Leu Lys Asp Phe His Lys
                405                 410                 415

Asp Glu Val Arg Ile Leu Gly Arg Glu Leu Gly Leu Pro Glu Glu Leu
            420                 425                 430

Val Ser Arg His Pro Phe Pro Gly Pro Gly Leu Ala Ile Arg Val Ile
        435                 440                 445

Cys Ala Glu Glu Pro Tyr Ile Cys Lys Asp Phe Pro Glu Thr Asn Asn
    450                 455                 460

Ile Leu Lys Ile Val Ala Asp Phe Ser Ala Ser Val Lys Lys Pro His
465                 470                 475                 480

Thr Leu Leu Gln Arg Val Lys Ala Cys Thr Thr Glu Glu Asp Gln Glu
                485                 490                 495

Lys Leu Met Gln Ile Thr Ser Leu His Ser Leu Asn Ala Phe Leu Leu
            500                 505                 510

Pro Ile Lys Thr Val Gly Val Gln Gly Asp Cys Arg Ser Tyr Ser Tyr
        515                 520                 525

Val Cys Gly Ile Ser Ser Lys Asp Glu Pro Asp Trp Glu Ser Leu Ile
    530                 535                 540

Phe Leu Ala Arg Leu Ile Pro Arg Met Cys His Asn Val Asn Arg Val
545                 550                 555                 560

Val Tyr Ile Phe Gly Pro Pro Val Lys Glu Pro Pro Thr Asp Val Thr
                565                 570                 575

Pro Thr Phe Leu Thr Thr Gly Val Leu Ser Thr Leu Arg Gln Ala Asp
            580                 585                 590

Phe Glu Ala His Asn Ile Leu Arg Glu Ser Gly Tyr Ala Gly Lys Ile
        595                 600                 605

Ser Gln Met Pro Val Ile Leu Thr Pro Leu His Phe Asp Arg Asp Pro
    610                 615                 620

Leu Gln Lys Gln Pro Ser Cys Gln Arg Ser Val Val Ile Arg Thr Phe
```

625 630 635 640

Ile Thr Ser Asp Phe Met Thr Gly Ile Pro Ala Thr Pro Gly Asn Glu
645 650 655

Ile Pro Val Glu Val Val Leu Lys Met Val Thr Glu Ile Lys Lys Ile
660 665 670

Pro Gly Ile Ser Arg Ile Met Tyr Asp Leu Thr Ser Lys Pro Pro Gly
675 680 685

Thr Thr Glu Trp Glu
690

<210> 76
<211> 143
<212> PRT
<213> Homo Sapiens

<400> 76

Met Ser Gly Arg Gly Lys Thr Gly Gly Lys Ala Arg Ala Lys Ala Lys
1 5 10 15

Ser Arg Ser Ser Arg Ala Gly Leu Gln Phe Pro Val Gly Arg Val His
20 25 30

Arg Leu Leu Arg Lys Gly His Tyr Ala Glu Arg Val Gly Ala Gly Ala
35 40 45

Pro Val Tyr Leu Ala Ala Val Leu Glu Tyr Leu Thr Ala Glu Ile Leu
50 55 60

Glu Leu Ala Gly Asn Ala Ala Arg Asp Asn Lys Lys Thr Arg Ile Ile
65 70 75 80

Pro Arg His Leu Gln Leu Ala Ile Arg Asn Asp Glu Glu Leu Asn Lys
85 90 95

Leu Leu Gly Gly Val Thr Ile Ala Gln Gly Gly Val Leu Pro Asn Ile
100 105 110

Gln Ala Val Leu Leu Pro Lys Lys Thr Ser Ala Thr Val Gly Pro Lys
115 120 125

Ala Pro Ser Gly Gly Lys Lys Ala Thr Gln Ala Ser Gln Glu Tyr
130 135 140

<210> 77
<211> 126
<212> PRT
<213> Homo Sapiens

<400> 77

Met Pro Glu Pro Ala Lys Ser Ala Pro Ala Pro Lys Lys Gly Ser Lys
1 5 10 15

Lys Ala Val Thr Lys Ala Gln Lys Lys Asp Gly Lys Lys Arg Lys Arg
20 25 30

Ser Arg Lys Glu Ser Tyr Ser Val Tyr Val Tyr Lys Val Leu Lys Gln
35 40 45

Val His Pro Asp Thr Gly Ile Ser Ser Lys Ala Met Gly Ile Met Asn
50 55 60

Ser Phe Val Asn Asp Ile Phe Glu Arg Ile Ala Gly Glu Ala Ser Arg
65 70 75 80

Leu Ala His Tyr Asn Lys Arg Ser Thr Ile Thr Ser Arg Glu Ile Gln
85 90 95

Thr Ala Val Arg Leu Leu Leu Pro Gly Glu Leu Ala Lys His Ala Val
100 105 110

Ser Glu Gly Thr Lys Ala Val Thr Lys Tyr Thr Ser Ser Lys
115 120 125

<210> 78
<211> 664
<212> PRT
<213> Homo Sapiens

<400> 78

Met Lys Thr Gly Pro Phe Phe Leu Cys Leu Leu Gly Thr Ala Ala Ala
1 5 10 15

Ile Pro Thr Asn Ala Arg Leu Leu Ser Asp His Ser Lys Pro Thr Ala
20 25 30

Glu Thr Val Ala Pro Asp Asn Thr Ala Ile Pro Ser Leu Trp Ala Glu
35 40 45

Ala Glu Glu Asn Glu Lys Glu Thr Ala Val Ser Thr Glu Asp Asp Ser
50 55 60

His His Lys Ala Glu Lys Ser Ser Val Leu Lys Ser Lys Glu Glu Ser
65 70 75 80

His Glu Gln Ser Ala Glu Gln Gly Lys Ser Ser Ser Gln Glu Leu Gly
85 90 95

Leu Lys Asp Gln Glu Asp Ser Asp Gly His Leu Ser Val Asn Leu Glu
100 105 110

Tyr Ala Pro Thr Glu Gly Thr Leu Asp Ile Lys Glu Asp Met Ile Glu
115 120 125

Pro Gln Glu Lys Lys Leu Ser Glu Asn Thr Asp Phe Leu Ala Pro Gly
130 135 140

Val Ser Ser Phe Thr Asp Ser Asn Gln Gln Glu Ser Ile Thr Lys Arg
145 150 155 160

Glu Glu Asn Gln Glu Gln Pro Arg Asn Tyr Ser His His Gln Leu Asn
165 170 175

Arg Ser Ser Lys His Ser Gln Gly Leu Arg Asp Gln Gly Asn Gln Glu

```
            180                 185                 190

Gln Asp Pro Asn Ile Ser Asn Gly Glu Glu Glu Glu Glu Lys Glu Pro
        195                 200                 205

Gly Glu Val Gly Thr His Asn Asp Asn Gln Glu Arg Lys Thr Glu Leu
    210                 215                 220

Pro Arg Glu His Ala Asn Ser Lys Gln Glu Glu Asp Asn Thr Gln Ser
225                 230                 235                 240

Asp Asp Ile Leu Glu Glu Ser Asp Gln Pro Thr Gln Val Ser Lys Met
                245                 250                 255

Gln Glu Asp Glu Phe Asp Gln Gly Asn Gln Glu Gln Glu Asp Asn Ser
            260                 265                 270

Asn Ala Glu Met Glu Glu Glu Asn Ala Ser Asn Val Asn Lys His Ile
        275                 280                 285

Gln Glu Thr Glu Trp Gln Ser Gln Glu Gly Lys Thr Gly Leu Glu Ala
    290                 295                 300

Ile Ser Asn His Lys Glu Thr Glu Glu Lys Thr Val Ser Glu Ala Leu
305                 310                 315                 320

Leu Met Glu Pro Thr Asp Asp Gly Asn Thr Thr Pro Arg Asn His Gly
                325                 330                 335

Val Asp Asp Asp Gly Asp Asp Asp Gly Asp Asp Gly Gly Thr Asp Gly
            340                 345                 350

Pro Arg His Ser Ala Ser Asp Asp Tyr Phe Ile Pro Ser Gln Ala Phe
        355                 360                 365

Leu Glu Ala Glu Arg Ala Gln Ser Ile Ala Tyr His Leu Lys Ile Glu
    370                 375                 380

Glu Gln Arg Glu Lys Val His Glu Asn Glu Asn Ile Gly Thr Thr Glu
385                 390                 395                 400

Pro Gly Glu His Gln Glu Ala Lys Lys Ala Glu Asn Ser Ser Asn Glu
                405                 410                 415

Glu Glu Thr Ser Ser Glu Gly Asn Met Arg Val His Ala Val Asp Ser
            420                 425                 430

Cys Met Ser Phe Gln Cys Lys Arg Gly His Ile Cys Lys Ala Asp Gln
        435                 440                 445

Gln Gly Lys Pro His Cys Val Cys Gln Asp Pro Val Thr Cys Pro Pro
    450                 455                 460

Thr Lys Pro Leu Asp Gln Val Cys Gly Thr Asp Asn Gln Thr Tyr Ala
465                 470                 475                 480

Ser Ser Cys His Leu Phe Ala Thr Lys Cys Arg Leu Glu Gly Thr Lys
                485                 490                 495

Lys Gly His Gln Leu Gln Leu Asp Tyr Phe Gly Ala Cys Lys Ser Ile
```

500 505 510

Pro Thr Cys Thr Asp Phe Glu Val Ile Gln Phe Pro Leu Arg Met Arg
515 520 525

Asp Trp Leu Lys Asn Ile Leu Met Gln Leu Tyr Glu Ala Asn Ser Glu
530 535 540

His Ala Gly Tyr Leu Asn Glu Lys Gln Arg Asn Lys Val Lys Lys Ile
545 550 555 560

Tyr Leu Asp Glu Lys Arg Leu Leu Ala Gly Asp His Pro Ile Asp Leu
565 570 575

Leu Leu Arg Asp Phe Lys Lys Asn Tyr His Met Tyr Val Tyr Pro Val
580 585 590

His Trp Gln Phe Ser Glu Leu Asp Gln His Pro Met Asp Arg Val Leu
595 600 605

Thr His Ser Glu Leu Ala Pro Leu Arg Ala Ser Leu Val Pro Met Glu
610 615 620

His Cys Ile Thr Arg Phe Phe Glu Glu Cys Asp Pro Asn Lys Asp Lys
625 630 635 640

His Ile Thr Leu Lys Glu Trp Gly His Cys Phe Gly Ile Lys Glu Glu
645 650 655

Asp Ile Asp Glu Asn Leu Leu Phe
660

<210> 79
<211> 460
<212> PRT
<213> Homo Sapiens

<400> 79

Ala Lys Leu Ala Thr Lys Ser Pro Thr Ile Thr Met Met Leu Ser Thr
1 5 10 15

Glu Gly Arg Glu Gly Phe Val Val Lys Val Arg Gly Leu Pro Trp Ser
20 25 30

Cys Ser Ala Asp Glu Val Met Arg Phe Phe Ser Asp Cys Lys Ile Gln
35 40 45

Asn Gly Thr Ser Gly Ile Arg Phe Ile Tyr Thr Arg Glu Gly Arg Pro
50 55 60

Ser Gly Glu Ala Phe Val Glu Leu Glu Ser Glu Glu Glu Val Lys Leu
65 70 75 80

Ala Leu Lys Lys Asp Arg Glu Thr Met Gly His Arg Tyr Val Glu Val
85 90 95

Phe Lys Ser Asn Ser Val Glu Met Asp Trp Val Leu Lys His Thr Gly
100 105 110

```
Pro Asn Ser Pro Asp Thr Ala Asn Asp Gly Phe Val Arg Leu Arg Gly
        115                 120                 125

Leu Pro Phe Gly Cys Ser Lys Glu Glu Ile Val Gln Phe Phe Ser Gly
    130                 135                 140

Leu Glu Ile Val Pro Asn Gly Met Thr Leu Pro Val Asp Phe Gln Gly
145                 150                 155                 160

Arg Ser Thr Gly Glu Ala Phe Val Gln Phe Ala Ser Gln Glu Ile Ala
                165                 170                 175

Glu Lys Ala Leu Lys Lys His Lys Glu Arg Ile Gly His Arg Tyr Ile
            180                 185                 190

Glu Ile Phe Lys Ser Ser Arg Ala Glu Val Arg Thr His Tyr Asp Pro
        195                 200                 205

Pro Arg Lys Leu Met Ala Met Gln Arg Pro Gly Pro Tyr Asp Arg Pro
    210                 215                 220

Gly Ala Gly Arg Gly Tyr Asn Ser Ile Gly Arg Gly Ala Gly Phe Glu
225                 230                 235                 240

Arg Met Arg Arg Gly Ala Tyr Gly Gly Gly Tyr Gly Gly Tyr Asp Asp
                245                 250                 255

Tyr Gly Gly Tyr Asn Asp Gly Tyr Gly Phe Gly Ser Asp Arg Phe Gly
            260                 265                 270

Arg Asp Leu Asn Tyr Cys Phe Ser Gly Met Ser Asp His Arg Tyr Gly
        275                 280                 285

Asp Gly Gly Ser Ser Phe Gln Ser Thr Thr Gly His Cys Val His Met
    290                 295                 300

Arg Gly Leu Pro Tyr Arg Ala Thr Glu Asn Asp Ile Tyr Asn Phe Phe
305                 310                 315                 320

Ser Pro Leu Asn Pro Met Arg Val His Ile Glu Ile Gly Pro Asp Gly
                325                 330                 335

Arg Val Thr Gly Glu Ala Asp Val Glu Phe Ala Thr His Glu Asp Ala
            340                 345                 350

Val Ala Ala Met Ala Lys Asp Lys Ala Asn Met Gln His Arg Tyr Val
        355                 360                 365

Glu Leu Phe Leu Asn Ser Thr Ala Gly Thr Ser Gly Gly Ala Tyr Asp
    370                 375                 380

His Ser Tyr Val Glu Leu Phe Leu Asn Ser Thr Ala Gly Ala Ser Gly
385                 390                 395                 400

Gly Ala Tyr Gly Ser Gln Met Met Gly Gly Met Gly Leu Ser Asn Gln
                405                 410                 415

Ser Ser Tyr Gly Gly Pro Ala Ser Gln Gln Leu Ser Gly Gly Tyr Gly
            420                 425                 430
```

```
Gly Gly Tyr Gly Gly Gln Ser Ser Met Ser Gly Tyr Asp Gln Val Leu
        435                 440                 445

Gln Glu Asn Ser Ser Asp Tyr Gln Ser Asn Leu Ala
    450                 455                 460

<210>  80
<211>  432
<212>  PRT
<213>  Homo Sapiens

<400>  80

Met Asp Glu Ala Val Gly Asp Leu Lys Gln Ala Leu Pro Cys Val Ala
1               5                   10                  15

Glu Ser Pro Thr Val His Val Glu Val His Gln Arg Gly Ser Ser Thr
            20                  25                  30

Ala Lys Lys Glu Asp Ile Asn Leu Ser Val Arg Lys Leu Leu Asn Arg
        35                  40                  45

His Asn Ile Val Phe Gly Asp Tyr Thr Trp Thr Glu Phe Asp Glu Pro
    50                  55                  60

Phe Leu Thr Arg Asn Val Gln Ser Val Ser Ile Ile Asp Thr Glu Leu
65                  70                  75                  80

Lys Val Lys Asp Ser Gln Pro Ile Asp Leu Ser Ala Cys Thr Val Ala
                85                  90                  95

Leu His Ile Phe Gln Leu Asn Glu Asp Gly Pro Ser Ser Glu Asn Leu
            100                 105                 110

Glu Glu Glu Thr Glu Asn Ile Ile Ala Ala Asn His Trp Val Leu Pro
        115                 120                 125

Ala Ala Glu Phe His Gly Leu Trp Asp Ser Leu Val Tyr Asp Val Glu
    130                 135                 140

Val Lys Ser His Leu Leu Asp Tyr Val Met Thr Thr Leu Leu Phe Ser
145                 150                 155                 160

Asp Lys Asn Val Asn Ser Asn Leu Ile Thr Trp Asn Arg Val Val Leu
                165                 170                 175

Leu His Gly Pro Pro Gly Thr Gly Lys Thr Ser Leu Cys Lys Ala Leu
            180                 185                 190

Ala Gln Lys Leu Thr Ile Arg Leu Ser Ser Arg Tyr Arg Tyr Gly Gln
        195                 200                 205

Leu Ile Glu Ile Asn Ser His Ser Leu Phe Ser Lys Trp Phe Ser Glu
    210                 215                 220

Ser Gly Lys Leu Val Thr Lys Met Phe Gln Lys Ile Gln Asp Leu Ile
225                 230                 235                 240

Asp Asp Lys Asp Ala Leu Val Phe Val Leu Ile Asp Glu Val Glu Ser
                245                 250                 255
```

```
Leu Thr Ala Ala Arg Asn Ala Cys Arg Ala Gly Thr Glu Pro Ser Asp
            260                 265                 270

Ala Ile Arg Val Val Asn Ala Val Leu Thr Gln Ile Asp Gln Ile Lys
        275                 280                 285

Arg His Ser Asn Val Val Ile Leu Thr Thr Ser Asn Ile Thr Glu Lys
    290                 295                 300

Ile Asp Val Ala Phe Val Asp Arg Ala Asp Ile Lys Gln Tyr Ile Gly
305                 310                 315                 320

Pro Pro Ser Ala Ala Ala Ile Phe Lys Ile Tyr Leu Ser Cys Leu Glu
                325                 330                 335

Glu Leu Met Lys Cys Gln Ile Ile Tyr Pro Arg Gln Gln Leu Leu Thr
            340                 345                 350

Leu Arg Glu Leu Glu Met Ile Gly Phe Ile Glu Asn Asn Val Ser Lys
        355                 360                 365

Leu Ser Leu Leu Leu Asn Asp Ile Ser Arg Lys Ser Glu Gly Leu Ser
    370                 375                 380

Gly Arg Val Leu Arg Lys Leu Pro Phe Leu Ala His Ala Leu Tyr Val
385                 390                 395                 400

Gln Ala Pro Thr Val Thr Ile Glu Gly Phe Leu Gln Ala Leu Ser Leu
                405                 410                 415

Ala Val Asp Lys Gln Phe Glu Glu Arg Lys Lys Leu Ala Ala Tyr Ile
            420                 425                 430
```

<210> 81
<211> 653
<212> PRT
<213> Homo Sapiens

<400> 81

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Met Arg Pro Leu Arg Pro Arg Ala Ala Leu Leu Ala Leu Leu Ala Ser
1               5                   10                  15

Leu Leu Ala Ala Pro Pro Val Ala Pro Ala Glu Ala Pro His Leu Val
            20                  25                  30

Gln Val Asp Ala Ala Arg Ala Leu Trp Pro Leu Arg Arg Phe Trp Arg
        35                  40                  45

Ser Thr Gly Phe Cys Pro Pro Leu Pro His Ser Gln Ala Asp Gln Tyr
    50                  55                  60

Val Leu Ser Trp Asp Gln Gln Leu Asn Leu Ala Tyr Val Gly Ala Val
65                  70                  75                  80

Pro His Arg Gly Ile Lys Gln Val Arg Thr His Trp Leu Leu Glu Leu
                85                  90                  95

Val Thr Thr Arg Gly Ser Thr Gly Arg Gly Leu Ser Tyr Asn Phe Thr
```

```
            100                 105                 110

His Leu Asp Gly Tyr Leu Asp Leu Leu Arg Glu Asn Gln Leu Leu Pro
        115                 120                 125

Gly Phe Glu Leu Met Gly Ser Ala Ser Gly His Phe Thr Asp Phe Glu
    130                 135                 140

Asp Lys Gln Gln Val Phe Glu Trp Lys Asp Leu Val Ser Ser Leu Ala
145                 150                 155                 160

Arg Arg Tyr Ile Gly Arg Tyr Gly Leu Ala His Val Ser Lys Trp Asn
                165                 170                 175

Phe Glu Thr Trp Asn Glu Pro Asp His His Asp Phe Asp Asn Val Ser
            180                 185                 190

Met Thr Met Gln Gly Phe Leu Asn Tyr Tyr Asp Ala Cys Ser Glu Gly
        195                 200                 205

Leu Arg Ala Ala Ser Pro Ala Leu Arg Leu Gly Gly Pro Gly Asp Ser
    210                 215                 220

Phe His Thr Pro Pro Arg Ser Pro Leu Ser Trp Gly Leu Leu Arg His
225                 230                 235                 240

Cys His Asp Gly Thr Asn Phe Phe Thr Gly Glu Ala Gly Val Arg Leu
                245                 250                 255

Asp Tyr Ile Ser Leu His Arg Lys Gly Ala Arg Ser Ser Ile Ser Ile
            260                 265                 270

Leu Glu Gln Glu Lys Val Val Ala Gln Gln Ile Arg Gln Leu Phe Pro
        275                 280                 285

Lys Phe Ala Asp Thr Pro Ile Tyr Asn Asp Glu Ala Asp Pro Leu Val
    290                 295                 300

Gly Trp Ser Leu Pro Gln Pro Trp Arg Ala Asp Val Thr Tyr Ala Ala
305                 310                 315                 320

Met Val Val Lys Val Ile Ala Gln His Gln Asn Leu Leu Leu Ala Asn
                325                 330                 335

Thr Thr Ser Ala Phe Pro Tyr Ala Leu Leu Ser Asn Asp Asn Ala Phe
            340                 345                 350

Leu Ser Tyr His Pro His Pro Phe Ala Gln Arg Thr Leu Thr Ala Arg
        355                 360                 365

Phe Gln Val Asn Asn Thr Arg Pro Pro His Val Gln Leu Leu Arg Lys
    370                 375                 380

Pro Val Leu Thr Ala Met Gly Leu Leu Ala Leu Leu Asp Glu Glu Gln
385                 390                 395                 400

Leu Trp Ala Glu Val Ser Gln Ala Gly Thr Val Leu Asp Ser Asn His
                405                 410                 415

Thr Val Gly Val Leu Ala Ser Ala His Arg Pro Gln Gly Pro Ala Asp
```

```
            420                 425                 430

Ala Trp Arg Ala Ala Val Leu Ile Tyr Ala Ser Asp Asp Thr Arg Ala
        435                 440                 445

His Pro Asn Arg Ser Val Ala Val Thr Leu Arg Leu Arg Gly Val Pro
    450                 455                 460

Pro Gly Pro Gly Leu Val Tyr Val Thr Arg Tyr Leu Asp Asn Gly Leu
465                 470                 475                 480

Cys Ser Pro Asp Gly Glu Trp Arg Arg Leu Gly Arg Pro Val Phe Pro
                485                 490                 495

Thr Ala Glu Gln Phe Arg Arg Met Arg Ala Ala Glu Asp Pro Val Ala
            500                 505                 510

Ala Ala Pro Arg Pro Leu Pro Ala Gly Gly Arg Leu Thr Leu Arg Pro
        515                 520                 525

Ala Leu Arg Leu Pro Ser Leu Leu Leu Val His Val Cys Ala Arg Pro
    530                 535                 540

Glu Lys Pro Pro Gly Gln Val Thr Arg Leu Arg Ala Leu Pro Leu Thr
545                 550                 555                 560

Gln Gly Gln Leu Val Leu Val Trp Ser Asp Glu His Val Gly Ser Lys
                565                 570                 575

Cys Leu Trp Thr Tyr Glu Ile Gln Phe Ser Gln Asp Gly Lys Ala Tyr
            580                 585                 590

Thr Pro Val Ser Arg Lys Pro Ser Thr Phe Asn Leu Phe Val Phe Ser
        595                 600                 605

Pro Asp Thr Gly Ala Val Ser Gly Ser Tyr Arg Val Arg Ala Leu Asp
    610                 615                 620

Tyr Trp Ala Arg Pro Gly Pro Phe Ser Asp Pro Val Pro Tyr Leu Glu
625                 630                 635                 640

Val Pro Val Pro Arg Gly Pro Pro Ser Pro Gly Asn Pro
                645                 650

<210>  82
<211>  153
<212>  PRT
<213>  Homo Sapiens

<400>  82

Met Gly Lys Ile Ser Ser Leu Pro Thr Gln Leu Phe Lys Cys Cys Phe
1               5                   10                  15

Cys Asp Phe Leu Lys Val Lys Met His Thr Met Ser Ser Ser His Leu
            20                  25                  30

Phe Tyr Leu Ala Leu Cys Leu Leu Thr Phe Thr Ser Ser Ala Thr Ala
        35                  40                  45
```

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
50 55 60

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
65 70 75 80

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
85 90 95

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
100 105 110

Lys Pro Ala Lys Ser Ala Arg Ser Val Arg Ala Gln Arg His Thr Asp
115 120 125

Met Pro Lys Thr Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly
130 135 140

Ser Ala Gly Asn Lys Asn Tyr Arg Met
145 150

<210> 83
<211> 1575
<212> PRT
<213> Homo Sapiens

<400> 83

Met Pro His Glu Glu Leu Pro Ser Leu Gln Arg Pro Arg Tyr Gly Ser
1 5 10 15

Ile Val Asp Asp Glu Arg Leu Ser Ala Glu Glu Met Asp Glu Arg Arg
20 25 30

Arg Gln Asn Ile Ala Tyr Glu Tyr Leu Cys His Leu Glu Glu Ala Lys
35 40 45

Arg Trp Met Glu Val Cys Leu Val Glu Glu Leu Pro Pro Thr Thr Glu
50 55 60

Leu Glu Glu Gly Leu Arg Asn Gly Val Tyr Leu Ala Lys Leu Ala Lys
65 70 75 80

Phe Phe Ala Pro Lys Met Val Ser Glu Lys Lys Ile Tyr Asp Val Glu
85 90 95

Gln Thr Arg Tyr Lys Lys Ser Gly Leu His Phe Arg His Thr Asp Asn
100 105 110

Thr Val Gln Trp Leu Arg Ala Met Glu Ser Ile Gly Leu Pro Lys Ile
115 120 125

Phe Tyr Pro Glu Thr Thr Asp Val Tyr Asp Arg Lys Asn Ile Pro Arg
130 135 140

Met Ile Tyr Cys Ile His Ala Leu Ser Leu Tyr Leu Phe Lys Leu Gly
145 150 155 160

Ile Ala Pro Gln Ile Gln Asp Leu Leu Gly Lys Val Asp Phe Thr Glu
165 170 175

```
Glu Glu Ile Ser Asn Met Arg Lys Glu Leu Glu Lys Tyr Gly Ile Gln
            180                 185                 190

Met Pro Ser Phe Ser Lys Ile Gly Gly Ile Leu Ala Asn Glu Leu Ser
        195                 200                 205

Val Asp Glu Ala Ala Leu His Ala Ala Val Ile Ala Ile Asn Glu Ala
    210                 215                 220

Val Glu Lys Gly Ile Ala Glu Gln Thr Val Val Thr Leu Arg Asn Pro
225                 230                 235                 240

Asn Ala Val Leu Thr Leu Val Asp Asp Asn Leu Ala Pro Glu Tyr Gln
                245                 250                 255

Lys Glu Leu Trp Asp Ala Lys Lys Lys Lys Glu Glu Asn Ala Arg Leu
            260                 265                 270

Lys Asn Ser Cys Ile Ser Glu Glu Glu Arg Asp Ala Tyr Glu Glu Leu
        275                 280                 285

Leu Thr Gln Ala Glu Ile Gln Gly Asn Ile Asn Lys Val Asn Arg Gln
    290                 295                 300

Ala Ala Val Asp His Ile Asn Ala Val Ile Pro Glu Gly Asp Pro Glu
305                 310                 315                 320

Asn Thr Leu Leu Ala Leu Lys Lys Pro Glu Ala Gln Leu Pro Ala Val
                325                 330                 335

Tyr Pro Phe Ala Ala Ala Met Tyr Gln Asn Glu Leu Phe Asn Leu Gln
            340                 345                 350

Lys Gln Asn Thr Met Asn Tyr Leu Ala His Glu Glu Leu Leu Ile Ala
        355                 360                 365

Val Glu Met Leu Ser Ala Val Ala Leu Leu Asn Gln Ala Leu Glu Ser
    370                 375                 380

Asn Asp Leu Val Ser Val Gln Asn Gln Leu Arg Ser Pro Ala Ile Gly
385                 390                 395                 400

Leu Asn Asn Leu Asp Lys Ala Tyr Val Glu Arg Tyr Ala Asn Thr Leu
                405                 410                 415

Leu Ser Val Lys Leu Glu Val Leu Ser Gln Gly Gln Asp Asn Leu Ser
            420                 425                 430

Trp Asn Glu Ile Gln Asn Cys Ile Asp Met Val Asn Ala Gln Ile Gln
        435                 440                 445

Glu Glu Asn Asp Arg Val Val Ala Val Gly Tyr Ile Asn Glu Ala Ile
    450                 455                 460

Asp Glu Gly Asn Pro Leu Arg Thr Leu Glu Thr Leu Leu Leu Pro Thr
465                 470                 475                 480

Ala Asn Ile Ser Asp Val Asp Pro Ala His Ala Gln His Tyr Gln Asp
                485                 490                 495
```

```
Val Leu Tyr His Ala Lys Ser Gln Lys Leu Gly Asp Ser Glu Ser Val
            500                 505                 510

Ser Lys Val Leu Trp Leu Asp Glu Ile Gln Gln Ala Val Asp Glu Ala
        515                 520                 525

Asn Val Asp Glu Asp Arg Ala Lys Gln Trp Val Thr Leu Val Val Asp
    530                 535                 540

Val Asn Gln Cys Leu Glu Gly Lys Lys Ser Ser Asp Ile Leu Ser Val
545                 550                 555                 560

Leu Lys Ser Ser Thr Ser Asn Ala Asn Asp Ile Ile Pro Glu Cys Ala
                565                 570                 575

Asp Lys Tyr Tyr Asp Ala Leu Val Lys Ala Lys Glu Leu Lys Ser Glu
            580                 585                 590

Arg Val Ser Ser Asp Gly Ser Trp Leu Lys Leu Asn Leu His Lys Lys
        595                 600                 605

Tyr Asp Tyr Tyr Tyr Asn Thr Asp Ser Lys Glu Ser Ser Trp Val Thr
    610                 615                 620

Pro Glu Ser Cys Phe Tyr Lys Glu Ser Trp Leu Thr Gly Lys Glu Ile
625                 630                 635                 640

Glu Asp Ile Ile Glu Glu Val Thr Val Gly Tyr Ile Arg Glu Asn Ile
                645                 650                 655

Trp Ser Ala Ser Glu Glu Leu Leu Leu Arg Phe Gln Ala Thr Ser Ser
            660                 665                 670

Gly Pro Ile Leu Arg Glu Glu Phe Glu Ala Arg Lys Ser Phe Leu His
        675                 680                 685

Glu Gln Glu Glu Asn Val Val Lys Ile Gln Ala Phe Trp Lys Gly Tyr
    690                 695                 700

Lys Gln Arg Lys Glu Tyr Met His Arg Arg Gln Thr Phe Ile Asp Asn
705                 710                 715                 720

Thr Asp Ser Val Val Lys Ile Gln Ser Trp Phe Arg Met Ala Thr Ala
                725                 730                 735

Arg Lys Ser Tyr Leu Ser Arg Leu Gln Tyr Phe Arg Asp His Asn Asn
            740                 745                 750

Glu Ile Val Lys Ile Gln Ser Leu Leu Arg Ala Asn Lys Ala Arg Asp
        755                 760                 765

Asp Tyr Lys Thr Leu Val Gly Ser Glu Asn Pro Pro Leu Thr Val Ile
    770                 775                 780

Arg Lys Phe Val Tyr Leu Leu Asp Gln Ser Asp Leu Asp Phe Gln Glu
785                 790                 795                 800

Glu Leu Glu Val Ala Arg Leu Arg Glu Glu Val Val Thr Lys Ile Arg
                805                 810                 815
```

```
Ala Asn Gln Gln Leu Glu Lys Asp Leu Asn Leu Met Asp Ile Lys Ile
            820                 825                 830

Gly Leu Leu Val Lys Asn Arg Ile Thr Leu Glu Asp Val Ile Ser His
        835                 840                 845

Ser Lys Lys Leu Asn Lys Lys Lys Gly Gly Glu Met Glu Ile Leu Asn
    850                 855                 860

Asn Thr Asp Asn Gln Gly Ile Lys Ser Leu Ser Lys Glu Arg Arg Lys
865                 870                 875                 880

Thr Leu Glu Thr Tyr Gln Gln Leu Phe Tyr Leu Leu Gln Thr Asn Pro
                885                 890                 895

Leu Tyr Leu Ala Lys Leu Ile Phe Gln Met Pro Gln Asn Lys Ser Thr
            900                 905                 910

Lys Phe Met Asp Thr Val Ile Phe Thr Leu Tyr Asn Tyr Ala Ser Asn
        915                 920                 925

Gln Arg Glu Glu Tyr Leu Leu Leu Lys Leu Phe Lys Thr Ala Leu Glu
    930                 935                 940

Glu Glu Ile Lys Ser Lys Val Asp Gln Val Gln Asp Ile Val Thr Gly
945                 950                 955                 960

Asn Pro Thr Val Ile Lys Met Val Val Ser Phe Asn Arg Gly Ala Arg
                965                 970                 975

Gly Gln Asn Thr Leu Arg Gln Leu Leu Ala Pro Val Val Lys Glu Ile
            980                 985                 990

Ile Asp Asp Lys Ser Leu Ile Ile  Asn Thr Asn Pro Val  Glu Val Tyr
        995                 1000                1005

Lys Ala  Trp Val Asn Gln Leu  Glu Thr Gln Thr Gly  Glu Ala Ser
    1010                1015                1020

Lys Leu  Pro Tyr Asp Val Thr  Thr Glu Gln Ala Leu  Thr Tyr Pro
    1025                1030                1035

Glu Val  Lys Asn Lys Leu Glu  Ala Ser Ile Glu Asn  Leu Arg Arg
    1040                1045                1050

Val Thr  Asp Lys Val Leu Asn  Ser Ile Ile Ser Ser  Leu Asp Leu
    1055                1060                1065

Leu Pro  Tyr Gly Leu Arg Tyr  Ile Ala Lys Val Leu  Lys Asn Ser
    1070                1075                1080

Ile His  Glu Lys Phe Pro Asp  Ala Thr Glu Asp Glu  Leu Leu Lys
    1085                1090                1095

Ile Val  Gly Asn Leu Leu Tyr  Tyr Arg Tyr Met Asn  Pro Ala Ile
    1100                1105                1110

Val Ala  Pro Asp Gly Phe Asp  Ile Ile Asp Met Thr  Ala Gly Gly
    1115                1120                1125
```

```
Gln Ile  Asn Ser Asp Gln Arg  Arg Asn Leu Gly Ser  Val Ala Lys
    1130                 1135                 1140

Val Leu  Gln His Ala Ala Ser  Asn Lys Leu Phe Glu  Gly Glu Asn
    1145                 1150                 1155

Glu His  Leu Ser Ser Met Asn  Asn Tyr Leu Ser Glu  Thr Tyr Gln
    1160                 1165                 1170

Glu Phe  Arg Lys Tyr Phe Lys  Glu Ala Cys Asn Val  Pro Glu Pro
    1175                 1180                 1185

Glu Glu  Lys Phe Asn Met Asp  Lys Tyr Thr Asp Leu  Val Thr Val
    1190                 1195                 1200

Ser Lys  Pro Val Ile Tyr Ile  Ser Ile Glu Glu Ile  Ile Ser Thr
    1205                 1210                 1215

His Ser  Leu Leu Leu Glu His  Gln Asp Ala Ile Ala  Pro Glu Lys
    1220                 1225                 1230

Asn Asp  Leu Leu Ser Glu Leu  Leu Gly Ser Leu Gly  Glu Val Pro
    1235                 1240                 1245

Thr Val  Glu Ser Phe Leu Gly  Glu Gly Ala Val Asp  Pro Asn Asp
    1250                 1255                 1260

Pro Asn  Lys Ala Asn Thr Leu  Ser Gln Leu Ser Lys  Thr Glu Ile
    1265                 1270                 1275

Ser Leu  Val Leu Thr Ser Lys  Tyr Asp Ile Glu Asp  Gly Glu Ala
    1280                 1285                 1290

Ile Asp  Ser Arg Ser Leu Met  Ile Lys Thr Lys Lys  Leu Ile Ile
    1295                 1300                 1305

Asp Val  Ile Arg Asn Gln Pro  Gly Asn Thr Leu Thr  Glu Ile Leu
    1310                 1315                 1320

Glu Thr  Pro Ala Thr Ala Gln  Gln Glu Val Asp His  Ala Thr Asp
    1325                 1330                 1335

Met Val  Ser Arg Ala Met Ile  Asp Ser Arg Thr Pro  Glu Glu Met
    1340                 1345                 1350

Lys His  Ser Gln Ser Met Ile  Glu Asp Ala Gln Leu  Pro Leu Glu
    1355                 1360                 1365

Gln Lys  Lys Arg Lys Ile Gln  Arg Asn Leu Arg Thr  Leu Glu Gln
    1370                 1375                 1380

Thr Gly  His Val Ser Ser Glu  Asn Lys Tyr Gln Asp  Ile Leu Asn
    1385                 1390                 1395

Glu Ile  Ala Lys Asp Ile Arg  Asn Gln Arg Ile Tyr  Arg Lys Leu
    1400                 1405                 1410

Arg Lys  Ala Glu Leu Ala Lys  Leu Gln Gln Thr Leu  Asn Ala Leu
    1415                 1420                 1425
```

```
Asn Lys  Lys Ala Ala Phe Tyr  Glu Glu Gln Ile Asn  Tyr Tyr Asp
    1430                 1435                 1440

Thr Tyr  Ile Lys Thr Cys Leu  Asp Asn Leu Lys Arg  Lys Asn Thr
    1445                 1450                 1455

Arg Arg  Ser Ile Lys Leu Asp  Gly Lys Gly Glu Pro  Lys Gly Ala
    1460                 1465                 1470

Lys Arg  Ala Lys Pro Val Lys  Tyr Thr Ala Ala Lys  Leu His Glu
    1475                 1480                 1485

Lys Gly  Val Leu Leu Asp Ile  Asp Asp Leu Gln Thr  Asn Gln Phe
    1490                 1495                 1500

Lys Asn  Val Thr Phe Asp Ile  Ile Ala Thr Glu Asp  Val Gly Ile
    1505                 1510                 1515

Phe Asp  Val Arg Ser Lys Phe  Leu Gly Val Glu Met  Glu Lys Val
    1520                 1525                 1530

Gln Leu  Asn Ile Gln Asp Leu  Leu Gln Met Gln Tyr  Glu Gly Val
    1535                 1540                 1545

Ala Val  Met Lys Met Phe Asp  Lys Val Lys Val Asn  Val Asn Leu
    1550                 1555                 1560

Leu Ile  Tyr Leu Leu Asn Lys  Lys Phe Tyr Gly Lys
    1565                 1570                 1575

<210>  84
<211>  165
<212>  PRT
<213>  Homo Sapiens

<400>  84

Met Gly Trp Asp Leu Thr Val Lys Met Leu Ala Gly Asn Glu Phe Gln
1               5                  10                  15

Val Ser Leu Ser Ser Ser Met Ser Val Ser Glu Leu Lys Ala Gln Ile
            20                  25                  30

Thr Gln Lys Ile Gly Val His Ala Phe Gln Gln Arg Leu Ala Val His
        35                  40                  45

Pro Ser Gly Val Ala Leu Gln Asp Arg Val Pro Leu Ala Ser Gln Gly
    50                  55                  60

Leu Gly Pro Gly Ser Thr Val Leu Leu Val Val Asp Lys Cys Asp Glu
65                  70                  75                  80

Pro Leu Ser Ile Leu Val Arg Asn Asn Lys Gly Arg Ser Ser Thr Tyr
                85                  90                  95

Glu Val Arg Leu Thr Gln Thr Val Ala His Leu Lys Gln Gln Val Ser
            100                 105                 110

Gly Leu Glu Gly Val Gln Asp Asp Leu Phe Trp Leu Thr Phe Glu Gly
```

```
        115                 120                 125

Lys Pro Leu Glu Asp Gln Leu Pro Leu Gly Glu Tyr Gly Leu Lys Pro
    130                 135                 140

Leu Ser Thr Val Phe Met Asn Leu Arg Leu Arg Gly Gly Gly Thr Glu
145                 150                 155                 160

Pro Gly Gly Arg Ser
                165
```

<210> 85
<211> 1218
<212> PRT
<213> Homo Sapiens

<400> 85

```
Met Arg Ser Pro Arg Thr Arg Gly Arg Ser Gly Arg Pro Leu Ser Leu
1               5                   10                  15

Leu Leu Ala Leu Leu Cys Ala Leu Arg Ala Lys Val Cys Gly Ala Ser
            20                  25                  30

Gly Gln Phe Glu Leu Glu Ile Leu Ser Met Gln Asn Val Asn Gly Glu
        35                  40                  45

Leu Gln Asn Gly Asn Cys Cys Gly Gly Ala Arg Asn Pro Gly Asp Arg
    50                  55                  60

Lys Cys Thr Arg Asp Glu Cys Asp Thr Tyr Phe Lys Val Cys Leu Lys
65                  70                  75                  80

Glu Tyr Gln Ser Arg Val Thr Ala Gly Gly Pro Cys Ser Phe Gly Ser
                85                  90                  95

Gly Ser Thr Pro Val Ile Gly Gly Asn Thr Phe Asn Leu Lys Ala Ser
            100                 105                 110

Arg Gly Asn Asp Pro Asn Arg Ile Val Leu Pro Phe Ser Phe Ala Trp
        115                 120                 125

Pro Arg Ser Tyr Thr Leu Leu Val Glu Ala Trp Asp Ser Ser Asn Asp
    130                 135                 140

Thr Val Gln Pro Asp Ser Ile Ile Glu Lys Ala Ser His Ser Gly Met
145                 150                 155                 160

Ile Asn Pro Ser Arg Gln Trp Gln Thr Leu Lys Gln Asn Thr Gly Val
                165                 170                 175

Ala His Phe Glu Tyr Gln Ile Arg Val Thr Cys Asp Asp Tyr Tyr Tyr
            180                 185                 190

Gly Phe Gly Cys Asn Lys Phe Cys Arg Pro Arg Asp Asp Phe Phe Gly
        195                 200                 205

His Tyr Ala Cys Asp Gln Asn Gly Asn Lys Thr Cys Met Glu Gly Trp
    210                 215                 220
```

```
Met Gly Pro Glu Cys Asn Arg Ala Ile Cys Arg Gln Gly Cys Ser Pro
225                 230                 235                 240

Lys His Gly Ser Cys Lys Leu Pro Gly Asp Cys Arg Cys Gln Tyr Gly
                245                 250                 255

Trp Gln Gly Leu Tyr Cys Asp Lys Cys Ile Pro His Pro Gly Cys Val
            260                 265                 270

His Gly Ile Cys Asn Glu Pro Trp Gln Cys Leu Cys Glu Thr Asn Trp
        275                 280                 285

Gly Gly Gln Leu Cys Asp Lys Asp Leu Asn Tyr Cys Gly Thr His Gln
    290                 295                 300

Pro Cys Leu Asn Gly Gly Thr Cys Ser Asn Thr Gly Pro Asp Lys Tyr
305                 310                 315                 320

Gln Cys Ser Cys Pro Glu Gly Tyr Ser Gly Pro Asn Cys Glu Ile Ala
                325                 330                 335

Glu His Ala Cys Leu Ser Asp Pro Cys His Asn Arg Gly Ser Cys Lys
            340                 345                 350

Glu Thr Ser Leu Gly Phe Glu Cys Glu Cys Ser Pro Gly Trp Thr Gly
        355                 360                 365

Pro Thr Cys Ser Thr Asn Ile Asp Asp Cys Ser Pro Asn Asn Cys Ser
    370                 375                 380

His Gly Gly Thr Cys Gln Asp Leu Val Asn Gly Phe Lys Cys Val Cys
385                 390                 395                 400

Pro Pro Gln Trp Thr Gly Lys Thr Cys Gln Leu Asp Ala Asn Glu Cys
                405                 410                 415

Glu Ala Lys Pro Cys Val Asn Ala Lys Ser Cys Lys Asn Leu Ile Ala
            420                 425                 430

Ser Tyr Tyr Cys Asp Cys Leu Pro Gly Trp Met Gly Gln Asn Cys Asp
        435                 440                 445

Ile Asn Ile Asn Asp Cys Leu Gly Gln Cys Gln Asn Asp Ala Ser Cys
    450                 455                 460

Arg Asp Leu Val Asn Gly Tyr Arg Cys Ile Cys Pro Pro Gly Tyr Ala
465                 470                 475                 480

Gly Asp His Cys Glu Arg Asp Ile Asp Glu Cys Ala Ser Asn Pro Cys
                485                 490                 495

Leu Asn Gly Gly His Cys Gln Asn Glu Ile Asn Arg Phe Gln Cys Leu
            500                 505                 510

Cys Pro Thr Gly Phe Ser Gly Asn Leu Cys Gln Leu Asp Ile Asp Tyr
        515                 520                 525

Cys Glu Pro Asn Pro Cys Gln Asn Gly Ala Gln Cys Tyr Asn Arg Ala
    530                 535                 540
```

```
Ser Asp Tyr Phe Cys Lys Cys Pro Glu Asp Tyr Glu Gly Lys Asn Cys
545                 550                 555                 560

Ser His Leu Lys Asp His Cys Arg Thr Thr Pro Cys Glu Val Ile Asp
                565                 570                 575

Ser Cys Thr Val Ala Met Ala Ser Asn Asp Thr Pro Glu Gly Val Arg
            580                 585                 590

Tyr Ile Ser Ser Asn Val Cys Gly Pro His Gly Lys Cys Lys Ser Gln
        595                 600                 605

Ser Gly Gly Lys Phe Thr Cys Asp Cys Asn Lys Gly Phe Thr Gly Thr
    610                 615                 620

Tyr Cys His Glu Asn Ile Asn Asp Cys Glu Ser Asn Pro Cys Arg Asn
625                 630                 635                 640

Gly Gly Thr Cys Ile Asp Gly Val Asn Ser Tyr Lys Cys Ile Cys Ser
                645                 650                 655

Asp Gly Trp Glu Gly Ala Tyr Cys Glu Thr Asn Ile Asn Asp Cys Ser
            660                 665                 670

Gln Asn Pro Cys His Asn Gly Gly Thr Cys Arg Asp Leu Val Asn Asp
        675                 680                 685

Phe Tyr Cys Asp Cys Lys Asn Gly Trp Lys Gly Lys Thr Cys His Ser
    690                 695                 700

Arg Asp Ser Gln Cys Asp Glu Ala Thr Cys Asn Asn Gly Gly Thr Cys
705                 710                 715                 720

Tyr Asp Glu Gly Asp Ala Phe Lys Cys Met Cys Pro Gly Gly Trp Glu
                725                 730                 735

Gly Thr Thr Cys Asn Ile Ala Arg Asn Ser Ser Cys Leu Pro Asn Pro
            740                 745                 750

Cys His Asn Gly Gly Thr Cys Val Val Asn Gly Glu Ser Phe Thr Cys
        755                 760                 765

Val Cys Lys Glu Gly Trp Glu Gly Pro Ile Cys Ala Gln Asn Thr Asn
    770                 775                 780

Asp Cys Ser Pro His Pro Cys Tyr Asn Ser Gly Thr Cys Val Asp Gly
785                 790                 795                 800

Asp Asn Trp Tyr Arg Cys Glu Cys Ala Pro Gly Phe Ala Gly Pro Asp
                805                 810                 815

Cys Arg Ile Asn Ile Asn Glu Cys Gln Ser Ser Pro Cys Ala Phe Gly
            820                 825                 830

Ala Thr Cys Val Asp Glu Ile Asn Gly Tyr Arg Cys Val Cys Pro Pro
        835                 840                 845

Gly His Ser Gly Ala Lys Cys Gln Glu Val Ser Gly Arg Pro Cys Ile
    850                 855                 860
```

```
Thr Met Gly Ser Val Ile Pro Asp Gly Ala Lys Trp Asp Asp Asp Cys
865                 870                 875                 880

Asn Thr Cys Gln Cys Leu Asn Gly Arg Ile Ala Cys Ser Lys Val Trp
                885                 890                 895

Cys Gly Pro Arg Pro Cys Leu Leu His Lys Gly His Ser Glu Cys Pro
            900                 905                 910

Ser Gly Gln Ser Cys Ile Pro Ile Leu Asp Asp Gln Cys Phe Val His
        915                 920                 925

Pro Cys Thr Gly Val Gly Glu Cys Arg Ser Ser Ser Leu Gln Pro Val
    930                 935                 940

Lys Thr Lys Cys Thr Ser Asp Ser Tyr Tyr Gln Asp Asn Cys Ala Asn
945                 950                 955                 960

Ile Thr Phe Thr Phe Asn Lys Glu Met Met Ser Pro Gly Leu Thr Thr
                965                 970                 975

Glu His Ile Cys Ser Glu Leu Arg Asn Leu Asn Ile Leu Lys Asn Val
            980                 985                 990

Ser Ala Glu Tyr Ser Ile Tyr Ile  Ala Cys Glu Pro Ser  Pro Ser Ala
        995                 1000                1005

Asn Asn  Glu Ile His Val Ala  Ile Ser Ala Glu Asp  Ile Arg Asp
    1010                1015                1020

Asp Gly  Asn Pro Ile Lys Glu  Ile Thr Asp Lys Ile  Ile Asp Leu
    1025                1030                1035

Val Ser  Lys Arg Asp Gly Asn  Ser Ser Leu Ile Ala  Ala Val Ala
    1040                1045                1050

Glu Val  Arg Val Gln Arg Arg  Pro Leu Lys Asn Arg  Thr Asp Phe
    1055                1060                1065

Leu Val  Pro Leu Leu Ser Ser  Val Leu Thr Val Ala  Trp Ile Cys
    1070                1075                1080

Cys Leu  Val Thr Ala Phe Tyr  Trp Cys Leu Arg Lys  Arg Arg Lys
    1085                1090                1095

Pro Gly  Ser His Thr His Ser  Ala Ser Glu Asp Asn  Thr Thr Asn
    1100                1105                1110

Asn Val  Arg Glu Gln Leu Asn  Gln Ile Lys Asn Pro  Ile Glu Lys
    1115                1120                1125

His Gly  Ala Asn Thr Val Pro  Ile Lys Asp Tyr Glu  Asn Lys Asn
    1130                1135                1140

Ser Lys  Met Ser Lys Ile Arg  Thr His Asn Ser Glu  Val Glu Glu
    1145                1150                1155

Asp Asp  Met Asp Lys His Gln  Gln Lys Ala Arg Phe  Ala Lys Gln
    1160                1165                1170
```

```
Pro Ala  Tyr Thr Leu Val Asp  Arg Glu Glu Lys Pro  Pro Asn Gly
    1175                 1180                 1185

Thr Pro  Thr Lys His Pro Asn  Trp Thr Asn Lys Gln  Asp Asn Arg
    1190                 1195                 1200

Asp Leu  Glu Ser Ala Gln Ser  Leu Asn Arg Met Glu  Tyr Ile Val
    1205                 1210                 1215
```

<210> 86
<211> 3110
<212> PRT
<213> Homo Sapiens

<400> 86

```
Met Pro Gly Ala Ala Gly Val Leu Leu Leu Leu Leu Leu Ser Gly Gly
1               5                  10                  15

Leu Gly Gly Val Gln Ala Gln Arg Pro Gln Gln Gln Arg Gln Ser Gln
            20                  25                  30

Ala His Gln Gln Arg Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser
        35                  40                  45

Asn Ala Leu Ile Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu
    50                  55                  60

Met Tyr Cys Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn
65                  70                  75                  80

Pro Gln Cys Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg
                85                  90                  95

His Pro Ile Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser
            100                 105                 110

Pro Ser Ile Lys Asn Gly Ile Glu Tyr His Tyr Val Thr Ile Thr Leu
        115                 120                 125

Asp Leu Gln Gln Val Phe Gln Ile Ala Tyr Val Ile Val Lys Ala Ala
    130                 135                 140

Asn Ser Pro Arg Pro Gly Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp
145                 150                 155                 160

Val Glu Tyr Lys Pro Trp Gln Tyr His Ala Val Thr Asp Thr Glu Cys
                165                 170                 175

Leu Thr Leu Tyr Asn Ile Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala
            180                 185                 190

Lys Asp Asp Glu Val Ile Cys Thr Ser Phe Tyr Ser Lys Ile His Pro
        195                 200                 205

Leu Glu Asn Gly Glu Ile His Ile Ser Leu Ile Asn Gly Arg Pro Ser
    210                 215                 220

Ala Asp Asp Pro Ser Pro Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr
225                 230                 235                 240
```

```
Ile Arg Leu Arg Phe Gln Arg Ile Arg Thr Leu Asn Ala Asp Leu Met
                245                 250                 255

Met Phe Ala His Lys Asp Pro Arg Glu Ile Asp Pro Ile Val Thr Arg
            260                 265                 270

Arg Tyr Tyr Tyr Ser Val Lys Asp Ile Ser Val Gly Gly Met Cys Ile
        275                 280                 285

Cys Tyr Gly His Ala Arg Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys
    290                 295                 300

Ser Arg Cys Glu Cys Glu His Asn Thr Cys Gly Asp Ser Cys Asp Gln
305                 310                 315                 320

Cys Cys Pro Gly Phe His Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu
                325                 330                 335

Thr Lys Thr Glu Cys Glu Ala Cys Asn Cys His Gly Lys Ala Glu Glu
            340                 345                 350

Cys Tyr Tyr Asp Glu Asn Val Ala Arg Arg Asn Leu Ser Leu Asn Ile
        355                 360                 365

Arg Gly Lys Tyr Ile Gly Gly Gly Val Cys Ile Asn Cys Thr Gln Asn
    370                 375                 380

Thr Ala Gly Ile Asn Cys Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro
385                 390                 395                 400

Lys Gly Val Ser Pro Asn Tyr Pro Arg Pro Cys Gln Pro Cys His Cys
                405                 410                 415

Asp Pro Ile Gly Ser Leu Asn Glu Val Cys Val Lys Asp Glu Lys His
            420                 425                 430

Ala Arg Arg Gly Leu Ala Pro Gly Ser Cys His Cys Lys Thr Gly Phe
        435                 440                 445

Gly Gly Val Ser Cys Asp Arg Cys Ala Arg Gly Tyr Thr Gly Tyr Pro
    450                 455                 460

Asp Cys Lys Ala Cys Asn Cys Ser Gly Leu Gly Ser Lys Asn Glu Asp
465                 470                 475                 480

Pro Cys Phe Gly Pro Cys Ile Cys Lys Glu Asn Val Glu Gly Gly Asp
                485                 490                 495

Cys Ser Arg Cys Lys Ser Gly Phe Phe Asn Leu Gln Glu Asp Asn Trp
            500                 505                 510

Lys Gly Cys Asp Glu Cys Phe Cys Ser Gly Val Ser Asn Arg Cys Gln
        515                 520                 525

Ser Ser Tyr Trp Thr Tyr Gly Lys Ile Gln Asp Met Ser Gly Trp Tyr
    530                 535                 540

Leu Thr Asp Leu Pro Gly Arg Ile Arg Val Ala Pro Gln Gln Asp Asp
545                 550                 555                 560
```

```
Leu Asp Ser Pro Gln Gln Ile Ser Ile Ser Asn Ala Glu Ala Arg Gln
                565                 570                 575

Ala Leu Pro His Ser Tyr Tyr Trp Ser Ala Pro Ala Pro Tyr Leu Gly
            580                 585                 590

Asn Lys Leu Pro Ala Val Gly Gly Gln Leu Thr Phe Thr Ile Ser Tyr
        595                 600                 605

Asp Leu Glu Glu Glu Glu Glu Asp Thr Glu Arg Val Leu Gln Leu Met
    610                 615                 620

Ile Ile Leu Glu Gly Asn Asp Leu Ser Ile Ser Thr Ala Gln Asp Glu
625                 630                 635                 640

Val Tyr Leu His Pro Ser Glu Glu His Thr Asn Val Leu Leu Leu Lys
                645                 650                 655

Glu Glu Ser Phe Thr Ile His Gly Thr His Phe Pro Val Arg Arg Lys
            660                 665                 670

Glu Phe Met Thr Val Leu Ala Asn Leu Lys Arg Val Leu Leu Gln Ile
        675                 680                 685

Thr Tyr Ser Phe Gly Met Asp Ala Ile Phe Arg Leu Ser Ser Val Asn
    690                 695                 700

Leu Glu Ser Ala Val Ser Tyr Pro Thr Asp Gly Ser Ile Ala Ala Ala
705                 710                 715                 720

Val Glu Val Cys Gln Cys Pro Pro Gly Tyr Thr Gly Ser Ser Cys Glu
                725                 730                 735

Ser Cys Trp Pro Arg His Arg Arg Val Asn Gly Thr Ile Phe Gly Gly
            740                 745                 750

Ile Cys Glu Pro Cys Gln Cys Phe Gly His Ala Glu Ser Cys Asp Asp
        755                 760                 765

Val Thr Gly Glu Cys Leu Asn Cys Lys Asp His Thr Gly Gly Pro Tyr
    770                 775                 780

Cys Asp Lys Cys Leu Pro Gly Phe Tyr Gly Glu Pro Thr Lys Gly Thr
785                 790                 795                 800

Ser Glu Asp Cys Gln Pro Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn
                805                 810                 815

Asn Phe Ser Pro Thr Cys His Leu Asp Arg Ser Leu Gly Leu Ile Cys
            820                 825                 830

Asp Gly Cys Pro Val Gly Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala
        835                 840                 845

Glu Gly Tyr Phe Gly Gln Pro Ser Val Pro Gly Gly Ser Cys Gln Pro
    850                 855                 860

Cys Gln Cys Asn Asp Asn Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp
865                 870                 875                 880
```

```
Ser Leu Ser Gly Ser Cys Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg
                885                 890                 895

Tyr Cys Glu Leu Cys Ala Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala
            900                 905                 910

Lys Asn Cys Gln Pro Cys Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu
        915                 920                 925

Val Cys His Ser Gln Thr Gly Gln Cys Glu Cys Arg Ala Asn Val Gln
    930                 935                 940

Gly Gln Arg Cys Asp Lys Cys Lys Ala Gly Thr Phe Gly Leu Gln Ser
945                 950                 955                 960

Ala Arg Gly Cys Val Pro Cys Asn Cys Asn Ser Phe Gly Ser Lys Ser
                965                 970                 975

Phe Asp Cys Glu Glu Ser Gly Gln Cys Trp Cys Gln Pro Gly Val Thr
            980                 985                 990

Gly Lys Lys Cys Asp Arg Cys Ala  His Gly Tyr Phe Asn  Phe Gln Glu
        995                 1000                1005

Gly Gly  Cys Thr Ala Cys Glu  Cys Ser His Leu Gly  Asn Asn Cys
    1010                1015                1020

Asp Pro  Lys Thr Gly Arg Cys  Ile Cys Pro Pro Asn  Thr Ile Gly
    1025                1030                1035

Glu Lys  Cys Ser Lys Cys Ala  Pro Asn Thr Trp Gly  His Ser Ile
    1040                1045                1050

Thr Thr  Gly Cys Lys Ala Cys  Asn Cys Ser Thr Val  Gly Ser Leu
    1055                1060                1065

Asp Phe  Gln Cys Asn Val Asn  Thr Gly Gln Cys Asn  Cys His Pro
    1070                1075                1080

Lys Phe  Ser Gly Ala Lys Cys  Thr Glu Cys Ser Arg  Gly His Trp
    1085                1090                1095

Asn Tyr  Pro Arg Cys Asn Leu  Cys Asp Cys Phe Leu  Pro Gly Thr
    1100                1105                1110

Asp Ala  Thr Thr Cys Asp Ser  Glu Thr Lys Lys Cys  Ser Cys Ser
    1115                1120                1125

Asp Gln  Thr Gly Gln Cys Thr  Cys Lys Val Asn Val  Glu Gly Ile
    1130                1135                1140

His Cys  Asp Arg Cys Arg Pro  Gly Lys Phe Gly Leu  Asp Ala Lys
    1145                1150                1155

Asn Pro  Leu Gly Cys Ser Ser  Cys Tyr Cys Phe Gly  Thr Thr Thr
    1160                1165                1170

Gln Cys  Ser Glu Ala Lys Gly  Leu Ile Arg Thr Trp  Val Thr Leu
    1175                1180                1185
```

```
Lys Ala  Glu Gln Thr Ile Leu  Pro Leu Val Asp Glu  Ala Leu Gln
    1190                 1195                 1200

His Thr  Thr Thr Lys Gly Ile  Val Phe Gln His Pro  Glu Ile Val
    1205                 1210                 1215

Ala His  Met Asp Leu Met Arg  Glu Asp Leu His Leu  Glu Pro Phe
    1220                 1225                 1230

Tyr Trp  Lys Leu Pro Glu Gln  Phe Glu Gly Lys Lys  Leu Met Ala
    1235                 1240                 1245

Tyr Gly  Gly Lys Leu Lys Tyr  Ala Ile Tyr Phe Glu  Ala Arg Glu
    1250                 1255                 1260

Glu Thr  Gly Phe Ser Thr Tyr  Asn Pro Gln Val Ile  Ile Arg Gly
    1265                 1270                 1275

Gly Thr  Pro Thr His Ala Arg  Ile Ile Val Arg His  Met Ala Ala
    1280                 1285                 1290

Pro Leu  Ile Gly Gln Leu Thr  Arg His Glu Ile Glu  Met Thr Glu
    1295                 1300                 1305

Lys Glu  Trp Lys Tyr Tyr Gly  Asp Asp Pro Arg Val  His Arg Thr
    1310                 1315                 1320

Val Thr  Arg Glu Asp Phe Leu  Asp Ile Leu Tyr Asp  Ile His Tyr
    1325                 1330                 1335

Ile Leu  Ile Lys Ala Thr Tyr  Gly Asn Phe Met Arg  Gln Ser Arg
    1340                 1345                 1350

Ile Ser  Glu Ile Ser Met Glu  Val Ala Glu Gln Gly  Arg Gly Thr
    1355                 1360                 1365

Thr Met  Thr Pro Pro Ala Asp  Leu Ile Glu Lys Cys  Asp Cys Pro
    1370                 1375                 1380

Leu Gly  Tyr Ser Gly Leu Ser  Cys Glu Ala Cys Leu  Pro Gly Phe
    1385                 1390                 1395

Tyr Arg  Leu Arg Ser Gln Pro  Gly Gly Arg Thr Pro  Gly Pro Thr
    1400                 1405                 1410

Leu Gly  Thr Cys Val Pro Cys  Gln Cys Asn Gly His  Ser Ser Leu
    1415                 1420                 1425

Cys Asp  Pro Glu Thr Ser Ile  Cys Gln Asn Cys Gln  His His Thr
    1430                 1435                 1440

Ala Gly  Asp Phe Cys Glu Arg  Cys Ala Leu Gly Tyr  Tyr Gly Ile
    1445                 1450                 1455

Val Lys  Gly Leu Pro Asn Asp  Cys Gln Gln Cys Ala  Cys Pro Leu
    1460                 1465                 1470

Ile Ser  Ser Ser Asn Asn Phe  Ser Pro Ser Cys Val  Ala Glu Gly
    1475                 1480                 1485
```

```
Leu Asp  Asp Tyr Arg Cys Thr  Ala Cys Pro Arg Gly  Tyr Glu Gly
    1490                 1495                 1500

Gln Tyr  Cys Glu Arg Cys Ala  Pro Gly Tyr Thr Gly  Ser Pro Gly
    1505                 1510                 1515

Asn Pro  Gly Gly Ser Cys Gln  Glu Cys Glu Cys Asp  Pro Tyr Gly
    1520                 1525                 1530

Ser Leu  Pro Val Pro Cys Asp  Pro Val Thr Gly Phe  Cys Thr Cys
    1535                 1540                 1545

Arg Pro  Gly Ala Thr Gly Arg  Lys Cys Asp Gly Cys  Lys His Trp
    1550                 1555                 1560

His Ala  Arg Glu Gly Trp Glu  Cys Val Phe Cys Gly  Asp Glu Cys
    1565                 1570                 1575

Thr Gly  Leu Leu Leu Gly Asp  Leu Ala Arg Leu Glu  Gln Met Val
    1580                 1585                 1590

Met Ser  Ile Asn Leu Thr Gly  Pro Leu Pro Ala Pro  Tyr Lys Met
    1595                 1600                 1605

Leu Tyr  Gly Leu Glu Asn Met  Thr Gln Glu Leu Lys  His Leu Leu
    1610                 1615                 1620

Ser Pro  Gln Arg Ala Pro Glu  Arg Leu Ile Gln Leu  Ala Glu Gly
    1625                 1630                 1635

Asn Leu  Asn Thr Leu Val Thr  Glu Met Asn Glu Leu  Leu Thr Arg
    1640                 1645                 1650

Ala Thr  Lys Val Thr Ala Asp  Gly Glu Gln Thr Gly  Gln Asp Ala
    1655                 1660                 1665

Glu Arg  Thr Asn Thr Arg Ala  Lys Ser Leu Gly Glu  Phe Ile Lys
    1670                 1675                 1680

Glu Leu  Ala Arg Asp Ala Glu  Ala Val Asn Glu Lys  Ala Ile Lys
    1685                 1690                 1695

Leu Asn  Glu Thr Leu Gly Thr  Arg Asp Glu Ala Phe  Glu Arg Asn
    1700                 1705                 1710

Leu Glu  Gly Leu Gln Lys Glu  Ile Asp Gln Met Ile  Lys Glu Leu
    1715                 1720                 1725

Arg Arg  Lys Asn Leu Glu Thr  Gln Lys Glu Ile Ala  Glu Asp Glu
    1730                 1735                 1740

Leu Val  Ala Ala Glu Ala Leu  Leu Lys Lys Val Lys  Lys Leu Phe
    1745                 1750                 1755

Gly Glu  Ser Arg Gly Glu Asn  Glu Glu Met Glu Lys  Asp Leu Arg
    1760                 1765                 1770

Glu Lys  Leu Ala Asp Tyr Lys  Asn Lys Val Asp Asp  Ala Trp Asp
    1775                 1780                 1785
```

```
Leu Leu  Arg Glu Ala Thr Asp  Lys Ile Arg Glu Ala  Asn Arg Leu
     1790                 1795                 1800

Phe Ala  Val Asn Gln Lys Asn  Met Thr Ala Leu Glu  Lys Lys Lys
     1805                 1810                 1815

Glu Ala  Val Glu Ser Gly Lys  Arg Gln Ile Glu Asn  Thr Leu Lys
     1820                 1825                 1830

Glu Gly  Asn Asp Ile Leu Asp  Glu Ala Asn Arg Leu  Ala Asp Glu
     1835                 1840                 1845

Ile Asn  Ser Ile Ile Asp Tyr  Val Glu Asp Ile Gln  Thr Lys Leu
     1850                 1855                 1860

Pro Pro  Met Ser Glu Glu Leu  Asn Asp Lys Ile Asp  Asp Leu Ser
     1865                 1870                 1875

Gln Glu  Ile Lys Asp Arg Lys  Leu Ala Glu Lys Val  Ser Gln Ala
     1880                 1885                 1890

Glu Ser  His Ala Ala Gln Leu  Asn Asp Ser Ser Ala  Val Leu Asp
     1895                 1900                 1905

Gly Ile  Leu Asp Glu Ala Lys  Asn Ile Ser Phe Asn  Ala Thr Ala
     1910                 1915                 1920

Ala Phe  Lys Ala Tyr Ser Asn  Ile Lys Asp Tyr Ile  Asp Glu Ala
     1925                 1930                 1935

Glu Lys  Val Ala Lys Glu Ala  Lys Asp Leu Ala His  Glu Ala Thr
     1940                 1945                 1950

Lys Leu  Ala Thr Gly Pro Arg  Gly Leu Leu Lys Glu  Asp Ala Lys
     1955                 1960                 1965

Gly Cys  Leu Gln Lys Ser Phe  Arg Ile Leu Asn Glu  Ala Lys Lys
     1970                 1975                 1980

Leu Ala  Asn Asp Val Lys Glu  Asn Glu Asp His Leu  Asn Gly Leu
     1985                 1990                 1995

Lys Thr  Arg Ile Glu Asn Ala  Asp Ala Arg Asn Gly  Asp Leu Leu
     2000                 2005                 2010

Arg Thr  Leu Asn Asp Thr Leu  Gly Lys Leu Ser Ala  Ile Pro Asn
     2015                 2020                 2025

Asp Thr  Ala Ala Lys Leu Gln  Ala Val Lys Asp Lys  Ala Arg Gln
     2030                 2035                 2040

Ala Asn  Asp Thr Ala Lys Asp  Val Leu Ala Gln Ile  Thr Glu Leu
     2045                 2050                 2055

His Gln  Asn Leu Asp Gly Leu  Lys Lys Asn Tyr Asn  Lys Leu Ala
     2060                 2065                 2070

Asp Ser  Val Ala Lys Thr Asn  Ala Val Val Lys Asp  Pro Ser Lys
     2075                 2080                 2085
```

```
Asn Lys  Ile Ile Ala Asp Ala  Asp Ala Thr Val Lys  Asn Leu Glu
    2090                 2095                 2100

Gln Glu  Ala Asp Arg Leu Ile  Asp Lys Leu Lys Pro  Ile Lys Glu
    2105                 2110                 2115

Leu Glu  Asp Asn Leu Lys Lys  Asn Ile Ser Glu Ile  Lys Glu Leu
    2120                 2125                 2130

Ile Asn  Gln Ala Arg Lys Gln  Ala Asn Ser Ile Lys  Val Ser Val
    2135                 2140                 2145

Ser Ser  Gly Gly Asp Cys Ile  Arg Thr Tyr Lys Pro  Glu Ile Lys
    2150                 2155                 2160

Lys Gly  Ser Tyr Asn Asn Ile  Val Val Asn Val Lys  Thr Ala Val
    2165                 2170                 2175

Ala Asp  Asn Leu Leu Phe Tyr  Leu Gly Ser Ala Lys  Phe Ile Asp
    2180                 2185                 2190

Phe Leu  Ala Ile Glu Met Arg  Lys Gly Lys Val Ser  Phe Leu Trp
    2195                 2200                 2205

Asp Val  Gly Ser Gly Val Gly  Arg Val Glu Tyr Pro  Asp Leu Thr
    2210                 2215                 2220

Ile Asp  Asp Ser Tyr Trp Tyr  Arg Ile Val Ala Ser  Arg Thr Gly
    2225                 2230                 2235

Arg Asn  Gly Thr Ile Ser Val  Arg Ala Leu Asp Gly  Pro Lys Ala
    2240                 2245                 2250

Ser Ile  Val Pro Ser Thr His  His Ser Thr Ser Pro  Pro Gly Tyr
    2255                 2260                 2265

Thr Ile  Leu Asp Val Asp Ala  Asn Ala Met Leu Phe  Val Gly Gly
    2270                 2275                 2280

Leu Thr  Gly Lys Leu Lys Lys  Ala Asp Ala Val Arg  Val Ile Thr
    2285                 2290                 2295

Phe Thr  Gly Cys Met Gly Glu  Thr Tyr Phe Asp Asn  Lys Pro Ile
    2300                 2305                 2310

Gly Leu  Trp Asn Phe Arg Glu  Lys Glu Gly Asp Cys  Lys Gly Cys
    2315                 2320                 2325

Thr Val  Ser Pro Gln Val Glu  Asp Ser Glu Gly Thr  Ile Gln Phe
    2330                 2335                 2340

Asp Gly  Glu Gly Tyr Ala Leu  Val Ser Arg Pro Ile  Arg Trp Tyr
    2345                 2350                 2355

Pro Asn  Ile Ser Thr Val Met  Phe Lys Phe Arg Thr  Phe Ser Ser
    2360                 2365                 2370

Ser Ala  Leu Leu Met Tyr Leu  Ala Thr Arg Asp Leu  Arg Asp Phe
    2375                 2380                 2385
```

Met Ser Val Glu Leu Thr Asp Gly His Ile Lys Val Ser Tyr Asp
2390 2395 2400

Leu Gly Ser Gly Met Ala Ser Val Val Ser Asn Gln Asn His Asn
2405 2410 2415

Asp Gly Lys Trp Lys Ser Phe Thr Leu Ser Arg Ile Gln Lys Gln
2420 2425 2430

Ala Asn Ile Ser Ile Val Asp Ile Asp Thr Asn Gln Glu Glu Asn
2435 2440 2445

Ile Ala Thr Ser Ser Ser Gly Asn Asn Phe Gly Leu Asp Leu Lys
2450 2455 2460

Ala Asp Asp Lys Ile Tyr Phe Gly Gly Leu Pro Thr Leu Arg Asn
2465 2470 2475

Leu Ser Met Lys Ala Arg Pro Glu Val Asn Leu Lys Lys Tyr Ser
2480 2485 2490

Gly Cys Leu Lys Asp Ile Glu Ile Ser Arg Thr Pro Tyr Asn Ile
2495 2500 2505

Leu Ser Ser Pro Asp Tyr Val Gly Val Thr Lys Gly Cys Ser Leu
2510 2515 2520

Glu Asn Val Tyr Thr Val Ser Phe Pro Lys Pro Gly Phe Val Glu
2525 2530 2535

Leu Ser Pro Val Pro Ile Asp Val Gly Thr Glu Ile Asn Leu Ser
2540 2545 2550

Phe Ser Thr Lys Asn Glu Ser Gly Ile Ile Leu Leu Gly Ser Gly
2555 2560 2565

Gly Thr Pro Ala Pro Pro Arg Arg Lys Arg Arg Gln Thr Gly Gln
2570 2575 2580

Ala Tyr Tyr Val Ile Leu Leu Asn Arg Gly Arg Leu Glu Val His
2585 2590 2595

Leu Ser Thr Gly Ala Arg Thr Met Arg Lys Ile Val Ile Arg Pro
2600 2605 2610

Glu Pro Asn Leu Phe His Asp Gly Arg Glu His Ser Val His Val
2615 2620 2625

Glu Arg Thr Arg Gly Ile Phe Thr Val Gln Val Asp Glu Asn Arg
2630 2635 2640

Arg Tyr Met Gln Asn Leu Thr Val Glu Gln Pro Ile Glu Val Lys
2645 2650 2655

Lys Leu Phe Val Gly Gly Ala Pro Pro Glu Phe Gln Pro Ser Pro
2660 2665 2670

Leu Arg Asn Ile Pro Pro Phe Glu Gly Cys Ile Trp Asn Leu Val
2675 2680 2685

Ile Asn Ser Val Pro Met Asp Phe Ala Arg Pro Val Ser Phe Lys
2690 2695 2700

Asn Ala Asp Ile Gly Arg Cys Ala His Gln Lys Leu Arg Glu Asp
2705 2710 2715

Glu Asp Gly Ala Ala Pro Ala Glu Ile Val Ile Gln Pro Glu Pro
2720 2725 2730

Val Pro Thr Pro Ala Phe Pro Thr Pro Thr Pro Val Leu Thr His
2735 2740 2745

Gly Pro Cys Ala Ala Glu Ser Glu Pro Ala Leu Leu Ile Gly Ser
2750 2755 2760

Lys Gln Phe Gly Leu Ser Arg Asn Ser His Ile Ala Ile Ala Phe
2765 2770 2775

Asp Asp Thr Lys Val Lys Asn Arg Leu Thr Ile Glu Leu Glu Val
2780 2785 2790

Arg Thr Glu Ala Glu Ser Gly Leu Leu Phe Tyr Met Ala Ala Ile
2795 2800 2805

Asn His Ala Asp Phe Ala Thr Val Gln Leu Arg Asn Gly Leu Pro
2810 2815 2820

Tyr Phe Ser Tyr Asp Leu Gly Ser Gly Asp Thr His Thr Met Ile
2825 2830 2835

Pro Thr Lys Ile Asn Asp Gly Gln Trp His Lys Ile Lys Ile Met
2840 2845 2850

Arg Ser Lys Gln Glu Gly Ile Leu Tyr Val Asp Gly Ala Ser Asn
2855 2860 2865

Arg Thr Ile Ser Pro Lys Lys Ala Asp Ile Leu Asp Val Val Gly
2870 2875 2880

Met Leu Tyr Val Gly Gly Leu Pro Ile Asn Tyr Thr Thr Arg Arg
2885 2890 2895

Ile Gly Pro Val Thr Tyr Ser Ile Asp Gly Cys Val Arg Asn Leu
2900 2905 2910

His Met Ala Glu Ala Pro Ala Asp Leu Glu Gln Pro Thr Ser Ser
2915 2920 2925

Phe His Val Gly Thr Cys Phe Ala Asn Ala Gln Arg Gly Thr Tyr
2930 2935 2940

Phe Asp Gly Thr Gly Phe Ala Lys Ala Val Gly Gly Phe Lys Val
2945 2950 2955

Gly Leu Asp Leu Leu Val Glu Phe Glu Phe Ala Thr Thr Thr Thr
2960 2965 2970

Thr Gly Val Leu Leu Gly Ile Ser Ser Gln Lys Met Asp Gly Met
2975 2980 2985

```
Gly Ile  Glu Met Ile Asp Glu  Lys Leu Met Phe His  Val Asp Asn
    2990                 2995                 3000

Gly Ala  Gly Arg Phe Thr Ala  Val Tyr Asp Ala Gly  Val Pro Gly
    3005                 3010                 3015

His Leu  Cys Asp Gly Gln Trp  His Lys Val Thr Ala  Asn Lys Ile
    3020                 3025                 3030

Lys His  Arg Ile Glu Leu Thr  Val Asp Gly Asn Gln  Val Glu Ala
    3035                 3040                 3045

Gln Ser  Pro Asn Pro Ala Ser  Thr Ser Ala Asp Thr  Asn Asp Pro
    3050                 3055                 3060

Val Phe  Val Gly Gly Phe Pro  Asp Asp Leu Lys Gln  Phe Gly Leu
    3065                 3070                 3075

Thr Thr  Ser Ile Pro Phe Arg  Gly Cys Ile Arg Ser  Leu Lys Leu
    3080                 3085                 3090

Thr Lys  Gly Thr Ala Ser His  Trp Arg Leu Ile Leu  Pro Arg Pro
    3095                 3100                 3105

Trp Asn
    3110
```

<210> 87
<211> 1798
<212> PRT
<213> Homo Sapiens

<400> 87

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Met Glu Leu Thr Ser Thr Glu Arg Gly Arg Gly Gln Pro Leu Pro Trp
1               5                  10                  15

Glu Leu Arg Leu Pro Leu Leu Leu Ser Val Leu Ala Ala Thr Leu Ala
            20                  25                  30

Gln Ala Pro Ala Pro Asp Val Pro Gly Cys Ser Arg Gly Ser Cys Tyr
        35                  40                  45

Pro Ala Thr Ala Asp Leu Leu Val Gly Arg Ala Asp Arg Leu Thr Ala
    50                  55                  60

Ser Ser Thr Cys Gly Leu Asn Gly Arg Gln Pro Tyr Cys Ile Val Ser
65                  70                  75                  80

His Leu Gln Asp Glu Lys Lys Cys Phe Leu Cys Asp Ser Arg Arg Pro
                85                  90                  95

Phe Ser Ala Arg Asp Asn Pro His Thr His Arg Ile Gln Asn Val Val
            100                 105                 110

Thr Ser Phe Ala Pro Gln Arg Arg Ala Ala Trp Trp Gln Ser Gln Asn
        115                 120                 125

Gly Ile Pro Ala Val Thr Ile Gln Leu Asp Leu Glu Ala Glu Phe His
```

```
    130                 135                 140

Phe Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg Pro Ala Ala Met
145                 150                 155                 160

Leu Val Glu Arg Ser Ala Asp Phe Gly Arg Thr Trp His Val Tyr Arg
                165                 170                 175

Tyr Phe Ser Tyr His Cys Gly Ala Asp Phe Pro Gly Val Pro Leu Ala
            180                 185                 190

Pro Pro Arg His Trp Asp Asp Val Val Cys Glu Ser Arg Tyr Ser Glu
        195                 200                 205

Ile Glu Pro Ser Thr Glu Gly Glu Val Ile Tyr Arg Val Leu Asp Pro
    210                 215                 220

Ala Ile Pro Ile Pro Asp Pro Tyr Ser Ser Arg Ile Gln Asn Leu Leu
225                 230                 235                 240

Lys Ile Thr Asn Leu Arg Val Asn Leu Thr Arg Leu His Thr Leu Gly
                245                 250                 255

Asp Asn Leu Leu Asp Pro Arg Arg Glu Ile Arg Glu Lys Tyr Tyr Tyr
            260                 265                 270

Ala Leu Tyr Glu Leu Val Val Arg Gly Asn Cys Phe Cys Tyr Gly His
        275                 280                 285

Ala Ser Glu Cys Ala Pro Ala Pro Gly Ala Pro Ala His Ala Glu Gly
    290                 295                 300

Met Val His Gly Ala Cys Ile Cys Lys His Asn Thr Arg Gly Leu Asn
305                 310                 315                 320

Cys Glu Gln Cys Gln Asp Phe Tyr Arg Asp Leu Pro Trp Arg Pro Ala
                325                 330                 335

Glu Asp Gly His Ser His Ala Cys Arg Lys Cys Asp Arg His Gly His
            340                 345                 350

Thr His Ser Cys His Phe Asp Met Ala Val Tyr Leu Gly Ser Gly Asn
        355                 360                 365

Val Ser Gly Gly Val Cys Asp Gly Cys Gln His Asn Thr Ala Trp Arg
    370                 375                 380

His Cys Glu Leu Cys Arg Pro Phe Phe Tyr Arg Asp Pro Thr Lys Asp
385                 390                 395                 400

Leu Arg Asp Pro Ala Val Cys Arg Ser Cys Asp Cys Asp Pro Met Gly
                405                 410                 415

Ser Gln Asp Gly Gly Arg Cys Asp Ser His Asp Asp Pro Ala Leu Gly
            420                 425                 430

Leu Val Ser Gly Gln Cys Arg Cys Lys Glu His Val Val Gly Thr Arg
        435                 440                 445

Cys Gln Gln Cys Arg Asp Gly Phe Phe Gly Leu Ser Ile Ser Asp Pro
```

```
    450                 455                 460

Ser Gly Cys Arg Arg Cys Gln Cys Asn Ala Arg Gly Thr Val Pro Gly
465                 470                 475                 480

Ser Thr Pro Cys Asp Pro Asn Ser Gly Ser Cys Tyr Cys Lys Arg Leu
                485                 490                 495

Val Thr Gly Arg Gly Cys Asp Arg Cys Leu Pro Gly His Trp Gly Leu
            500                 505                 510

Ser Leu Asp Leu Leu Gly Cys Arg Pro Cys Asp Cys Asp Val Gly Gly
        515                 520                 525

Ala Leu Asp Pro Gln Cys Asp Glu Gly Thr Gly Gln Cys His Cys Arg
    530                 535                 540

Gln His Met Val Gly Arg Arg Cys Glu Gln Val Gln Pro Gly Tyr Phe
545                 550                 555                 560

Arg Pro Phe Leu Asp His Leu Ile Trp Glu Ala Glu Asn Thr Arg Gly
                565                 570                 575

Gln Val Leu Asp Val Val Glu Arg Leu Val Thr Pro Gly Glu Thr Pro
            580                 585                 590

Ser Trp Thr Gly Ser Gly Phe Val Arg Leu Gln Glu Gly Gln Thr Leu
        595                 600                 605

Glu Phe Leu Val Ala Ser Val Pro Asn Ala Met Asp Tyr Asp Leu Leu
    610                 615                 620

Leu Arg Leu Glu Pro Gln Val Pro Glu Gln Trp Ala Glu Leu Glu Leu
625                 630                 635                 640

Ile Val Gln Arg Pro Gly Pro Val Pro Ala His Ser Leu Cys Gly His
                645                 650                 655

Leu Val Pro Arg Asp Asp Arg Ile Gln Gly Thr Leu Gln Pro His Ala
            660                 665                 670

Arg Tyr Leu Ile Phe Pro Asn Pro Val Cys Leu Glu Pro Gly Ile Ser
        675                 680                 685

Tyr Lys Leu His Leu Lys Leu Val Arg Thr Gly Gly Ser Ala Gln Pro
    690                 695                 700

Glu Thr Pro Tyr Ser Gly Pro Gly Leu Leu Ile Asp Ser Leu Val Leu
705                 710                 715                 720

Leu Pro Arg Val Leu Val Leu Glu Met Phe Ser Gly Gly Asp Ala Ala
                725                 730                 735

Ala Leu Glu Arg Gln Ala Thr Phe Glu Arg Tyr Gln Cys His Glu Glu
            740                 745                 750

Gly Leu Val Pro Ser Lys Thr Ser Pro Ser Glu Ala Cys Ala Pro Leu
        755                 760                 765

Leu Ile Ser Leu Ser Thr Leu Ile Tyr Asn Gly Ala Leu Pro Cys Gln
```

```
    770                 775                 780

Cys Asn Pro Gln Gly Ser Leu Ser Ser Glu Cys Asn Pro His Gly Gly
785                 790                 795                 800

Gln Cys Leu Cys Lys Pro Gly Val Val Gly Arg Arg Cys Asp Thr Cys
                805                 810                 815

Ala Pro Gly Tyr Tyr Gly Phe Gly Pro Thr Gly Cys Gln Ala Cys Gln
            820                 825                 830

Cys Ser Pro Arg Gly Ala Leu Ser Ser Leu Cys Glu Arg Thr Ser Gly
        835                 840                 845

Gln Cys Leu Cys Arg Thr Gly Ala Phe Gly Leu Arg Cys Asp Ala Cys
    850                 855                 860

Gln Arg Gly Gln Trp Gly Phe Pro Ser Cys Arg Pro Cys Val Cys Asn
865                 870                 875                 880

Gly His Ala Asp Glu Cys Asn Thr His Thr Gly Ala Cys Leu Gly Cys
                885                 890                 895

Arg Asp Leu Thr Gly Gly Glu His Cys Glu Arg Cys Ile Ala Gly Phe
            900                 905                 910

His Gly Asp Pro Arg Leu Pro Tyr Gly Ala Gln Cys Arg Pro Cys Pro
        915                 920                 925

Cys Pro Glu Gly Pro Gly Ser Gln Arg His Phe Ala Thr Ser Cys His
    930                 935                 940

Gln Asp Glu Tyr Ser Gln Gln Ile Val Cys His Cys Arg Ala Gly Tyr
945                 950                 955                 960

Thr Gly Leu Arg Cys Glu Ala Cys Ala Pro Gly Gln Phe Gly Asp Pro
                965                 970                 975

Ser Arg Pro Gly Gly Arg Cys Gln Leu Cys Glu Cys Ser Gly Asn Ile
            980                 985                 990

Asp Pro Met Asp Pro Asp Ala Cys  Asp Pro His Pro Gly  Gln Cys Leu
        995                 1000                1005

Arg Cys  Leu His His Thr Glu  Gly Pro His Cys Ala  His Ser Lys
    1010                1015                1020

Pro Gly  Phe His Gly Gln Ala  Ala Arg Gln Ser Cys  His Arg Cys
    1025                1030                1035

Thr Cys  Asn Leu Leu Gly Thr  Asn Pro Gln Gln Cys  Pro Ser Pro
    1040                1045                1050

Asp Gln  Cys His Cys Asp Pro  Ser Ser Gly Gln Cys  Pro Cys Leu
    1055                1060                1065

Pro Asn  Val Gln Ala Leu Ala  Val Asp Arg Cys Ala  Pro Asn Phe
    1070                1075                1080

Trp Asn  Leu Thr Ser Gly His  Gly Cys Gln Pro Cys  Ala Cys Leu
```

```
    1085                1090                1095

Pro Ser  Pro Glu Glu Gly Pro  Thr Cys Asn Glu Phe  Thr Gly Gln
    1100                1105                1110

Cys His  Cys Leu Cys Gly Phe  Gly Gly Arg Thr Cys  Ser Glu Cys
    1115                1120                1125

Gln Glu  Leu His Trp Gly Asp  Pro Gly Leu Gln Cys  His Ala Cys
    1130                1135                1140

Asp Cys  Asp Ser Arg Gly Ile  Asp Thr Pro Gln Cys  His Arg Phe
    1145                1150                1155

Thr Gly  His Cys Thr Cys Arg  Pro Gly Val Ser Gly  Val Arg Cys
    1160                1165                1170

Asp Gln  Cys Ala Arg Gly Phe  Ser Gly Ile Phe Pro  Ala Cys His
    1175                1180                1185

Pro Cys  His Ala Cys Phe Gly  Asp Trp Asp Arg Val  Val Gln Asp
    1190                1195                1200

Leu Ala  Ala Arg Thr Gln Arg  Leu Glu Gln Arg Ala  Gln Glu Leu
    1205                1210                1215

Gln Gln  Thr Gly Val Leu Gly  Ala Phe Glu Ser Ser  Phe Trp His
    1220                1225                1230

Met Gln  Glu Lys Leu Gly Ile  Val Gln Gly Ile Val  Gly Ala Arg
    1235                1240                1245

Asn Thr  Ser Ala Ala Ser Thr  Ala Gln Leu Val Glu  Ala Thr Glu
    1250                1255                1260

Glu Leu  Arg Arg Glu Ile Gly  Glu Ala Thr Glu His  Leu Thr Gln
    1265                1270                1275

Leu Glu  Ala Asp Leu Thr Asp  Val Gln Asp Glu Asn  Phe Asn Ala
    1280                1285                1290

Asn His  Ala Leu Ser Gly Leu  Glu Arg Asp Arg Leu  Ala Leu Asn
    1295                1300                1305

Leu Thr  Leu Arg Gln Leu Asp  Gln His Leu Asp Leu  Leu Lys His
    1310                1315                1320

Ser Asn  Phe Leu Gly Ala Tyr  Asp Ser Ile Arg His  Ala His Ser
    1325                1330                1335

Gln Ser  Ala Glu Ala Glu Arg  Arg Ala Asn Thr Ser  Ala Leu Ala
    1340                1345                1350

Val Pro  Ser Pro Val Ser Asn  Ser Ala Ser Ala Arg  His Arg Thr
    1355                1360                1365

Glu Ala  Leu Met Asp Ala Gln  Lys Glu Asp Phe Asn  Ser Lys His
    1370                1375                1380

Met Ala  Asn Gln Arg Ala Leu  Gly Lys Leu Ser Ala  His Thr His
```

```
    1385                1390                1395

Thr Leu  Ser Leu Thr Asp Ile  Asn Glu Leu Val Cys  Gly Ala Gln
    1400                1405                1410

Gly Leu  His His Asp Arg Thr  Ser Pro Cys Gly Gly  Ala Gly Cys
    1415                1420                1425

Arg Asp  Glu Asp Gly Gln Pro  Arg Cys Gly Gly Leu  Ser Cys Asn
    1430                1435                1440

Gly Ala  Ala Ala Thr Ala Asp  Leu Ala Leu Gly Arg  Ala Arg His
    1445                1450                1455

Thr Gln  Ala Glu Leu Gln Arg  Ala Leu Ala Glu Gly  Gly Ser Ile
    1460                1465                1470

Leu Ser  Arg Val Ala Glu Thr  Arg Arg Gln Ala Ser  Glu Ala Gln
    1475                1480                1485

Gln Arg  Ala Gln Ala Ala Leu  Asp Lys Ala Asn Ala  Ser Arg Gly
    1490                1495                1500

Gln Val  Glu Gln Ala Asn Gln  Glu Leu Gln Glu Leu  Ile Gln Ser
    1505                1510                1515

Val Lys  Asp Phe Leu Asn Gln  Glu Gly Ala Asp Pro  Asp Ser Ile
    1520                1525                1530

Glu Met  Val Ala Thr Arg Val  Leu Glu Leu Ser Ile  Pro Ala Ser
    1535                1540                1545

Ala Glu  Gln Ile Gln His Leu  Ala Gly Ala Ile Ala  Glu Arg Val
    1550                1555                1560

Arg Ser  Leu Ala Asp Val Asp  Ala Ile Leu Ala Arg  Thr Val Gly
    1565                1570                1575

Asp Val  Arg Arg Ala Glu Gln  Leu Leu Gln Asp Ala  Arg Arg Ala
    1580                1585                1590

Arg Ser  Trp Ala Glu Asp Glu  Lys Gln Lys Ala Glu  Thr Val Gln
    1595                1600                1605

Ala Ala  Leu Glu Glu Ala Gln  Arg Ala Gln Gly Ile  Ala Gln Gly
    1610                1615                1620

Ala Ile  Arg Gly Ala Val Ala  Asp Thr Arg Asp Thr  Glu Gln Thr
    1625                1630                1635

Leu Tyr  Gln Val Gln Glu Arg  Met Ala Gly Ala Glu  Arg Ala Leu
    1640                1645                1650

Ser Ser  Ala Gly Glu Arg Ala  Arg Gln Leu Asp Ala  Leu Leu Glu
    1655                1660                1665

Ala Leu  Lys Leu Lys Arg Ala  Gly Asn Ser Leu Ala  Ala Ser Thr
    1670                1675                1680

Ala Glu  Glu Thr Ala Gly Ser  Ala Gln Gly Arg Ala  Gln Glu Ala
```

1685 1690 1695

Glu Gln Leu Leu Arg Gly Pro Leu Gly Asp Gln Tyr Gln Thr Val
1700 1705 1710

Lys Ala Leu Ala Glu Arg Lys Ala Gln Gly Val Leu Ala Ala Gln
1715 1720 1725

Ala Arg Ala Glu Gln Leu Pro Asp Glu Ala Arg Asp Leu Leu Gln
1730 1735 1740

Ala Ala Gln Asp Lys Leu Gln Arg Leu Gln Glu Leu Glu Gly Thr
1745 1750 1755

Tyr Glu Glu Asn Glu Arg Ala Leu Glu Ser Lys Ala Ala Gln Leu
1760 1765 1770

Asp Gly Leu Glu Ala Arg Met Arg Ser Val Leu Gln Ala Ile Asn
1775 1780 1785

Leu Gln Val Gln Ile Tyr Asn Thr Cys Gln
1790 1795

<210> 88
<211> 615
<212> PRT
<213> Homo Sapiens

<400> 88

Met Pro Ser Arg Lys Phe Ala Asp Gly Glu Val Val Arg Gly Arg Trp
1 5 10 15

Pro Gly Ser Ser Leu Tyr Tyr Glu Val Glu Ile Leu Ser His Asp Ser
20 25 30

Thr Ser Gln Leu Tyr Thr Val Lys Tyr Lys Asp Gly Thr Glu Leu Glu
35 40 45

Leu Lys Glu Asn Asp Ile Lys Pro Leu Thr Ser Phe Arg Gln Arg Lys
50 55 60

Gly Gly Ser Thr Ser Ser Ser Pro Ser Arg Arg Arg Gly Ser Arg Ser
65 70 75 80

Arg Ser Arg Ser Arg Ser Pro Gly Arg Pro Pro Lys Ser Ala Arg Arg
85 90 95

Ser Ala Ser Ala Ser His Gln Ala Asp Ile Lys Glu Ala Arg Arg Glu
100 105 110

Val Glu Val Lys Leu Thr Pro Leu Ile Leu Lys Pro Phe Gly Asn Ser
115 120 125

Ile Ser Arg Tyr Asn Gly Glu Pro Glu His Ile Glu Arg Asn Asp Ala
130 135 140

Pro His Lys Asn Thr Gln Glu Lys Phe Ser Leu Ser Gln Glu Ser Ser
145 150 155 160

```
Tyr Ile Ala Thr Gln Tyr Ser Leu Arg Pro Arg Arg Glu Glu Val Lys
                165                 170                 175

Leu Lys Glu Ile Asp Ser Lys Glu Glu Lys Tyr Val Ala Lys Glu Leu
            180                 185                 190

Ala Val Arg Thr Phe Glu Val Thr Pro Ile Arg Ala Lys Asp Leu Glu
        195                 200                 205

Phe Gly Gly Val Pro Gly Val Phe Leu Ile Met Phe Gly Leu Pro Val
    210                 215                 220

Phe Leu Phe Leu Leu Leu Leu Met Cys Lys Gln Lys Asp Pro Ser Leu
225                 230                 235                 240

Leu Asn Phe Pro Pro Pro Leu Pro Ala Leu Tyr Glu Leu Trp Glu Thr
                245                 250                 255

Arg Val Phe Gly Val Tyr Leu Leu Trp Phe Leu Ile Gln Val Leu Phe
            260                 265                 270

Tyr Leu Leu Pro Ile Gly Lys Val Val Glu Gly Thr Pro Leu Ile Asp
        275                 280                 285

Gly Arg Arg Leu Lys Tyr Arg Leu Asn Gly Phe Tyr Pro Phe Ile Leu
    290                 295                 300

Thr Ser Ala Val Ile Gly Thr Ser Leu Phe Gln Gly Val Glu Phe His
305                 310                 315                 320

Tyr Val Tyr Ser His Phe Leu Gln Phe Ala Leu Ala Ala Thr Val Phe
                325                 330                 335

Cys Val Val Leu Ser Val Tyr Leu Tyr Met Arg Ser Leu Lys Ala Pro
            340                 345                 350

Arg Asn Asp Leu Ser Pro Ala Ser Ser Gly Asn Ala Val Tyr Asp Phe
        355                 360                 365

Phe Ile Gly Arg Glu Leu Asn Pro Arg Ile Gly Thr Phe Asp Leu Lys
    370                 375                 380

Tyr Phe Cys Glu Leu Arg Pro Gly Leu Ile Gly Trp Val Val Ile Asn
385                 390                 395                 400

Leu Val Met Leu Leu Ala Glu Met Lys Ile Gln Asp Arg Ala Val Pro
                405                 410                 415

Ser Leu Ala Met Ile Leu Val Asn Ser Phe Gln Leu Leu Tyr Val Val
            420                 425                 430

Asp Ala Leu Trp Asn Glu Glu Ala Leu Leu Thr Thr Met Asp Ile Ile
        435                 440                 445

His Asp Gly Phe Gly Phe Met Leu Ala Phe Gly Asp Leu Val Trp Val
    450                 455                 460

Pro Phe Ile Tyr Ser Phe Gln Ala Phe Tyr Leu Val Ser His Pro Asn
465                 470                 475                 480
```

```
Glu Val Ser Trp Pro Met Ala Ser Leu Ile Ile Val Leu Lys Leu Cys
                485                 490                 495

Gly Tyr Val Ile Phe Arg Gly Ala Asn Ser Gln Lys Asn Ala Phe Arg
            500                 505                 510

Lys Asn Pro Ser Asp Pro Lys Leu Ala His Leu Lys Thr Ile His Thr
        515                 520                 525

Ser Ser Gly Lys Asn Leu Leu Val Ser Gly Trp Trp Gly Phe Val Arg
    530                 535                 540

His Pro Asn Tyr Leu Gly Asp Leu Ile Met Ala Leu Ala Trp Ser Leu
545                 550                 555                 560

Pro Cys Gly Phe Asn His Ile Leu Pro Tyr Phe Tyr Ile Ile Tyr Phe
                565                 570                 575

Thr Met Leu Leu Val His Arg Glu Ala Arg Asp Glu Tyr His Cys Lys
            580                 585                 590

Lys Lys Tyr Gly Val Ala Trp Glu Lys Tyr Cys Gln Arg Val Pro Tyr
        595                 600                 605

Arg Ile Phe Pro Tyr Ile Tyr
    610                 615
```

<210> 89
<211> 660
<212> PRT
<213> Homo Sapiens

<400> 89

```
Met Glu Ala Leu Met Ala Arg Gly Ala Leu Thr Gly Pro Leu Arg Ala
1               5                   10                  15

Leu Cys Leu Leu Gly Cys Leu Leu Ser His Ala Ala Ala Ala Pro Ser
            20                  25                  30

Pro Ile Ile Lys Phe Pro Gly Asp Val Ala Pro Lys Thr Asp Lys Glu
        35                  40                  45

Leu Ala Val Gln Tyr Leu Asn Thr Phe Tyr Gly Cys Pro Lys Glu Ser
    50                  55                  60

Cys Asn Leu Phe Val Leu Lys Asp Thr Leu Lys Lys Met Gln Lys Phe
65                  70                  75                  80

Phe Gly Leu Pro Gln Thr Gly Asp Leu Asp Gln Asn Thr Ile Glu Thr
                85                  90                  95

Met Arg Lys Pro Arg Cys Gly Asn Pro Asp Val Ala Asn Tyr Asn Phe
            100                 105                 110

Phe Pro Arg Lys Pro Lys Trp Asp Lys Asn Gln Ile Thr Tyr Arg Ile
        115                 120                 125

Ile Gly Tyr Thr Pro Asp Leu Asp Pro Glu Thr Val Asp Asp Ala Phe
    130                 135                 140
```

```
Ala Arg Ala Phe Gln Val Trp Ser Asp Val Thr Pro Leu Arg Phe Ser
145                 150                 155                 160

Arg Ile His Asp Gly Glu Ala Asp Ile Met Ile Asn Phe Gly Arg Trp
                165                 170                 175

Glu His Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala
            180                 185                 190

His Ala Phe Ala Pro Gly Thr Gly Val Gly Gly Asp Ser His Phe Asp
        195                 200                 205

Asp Asp Glu Leu Trp Thr Leu Gly Glu Gly Gln Val Val Arg Val Lys
    210                 215                 220

Tyr Gly Asn Ala Asp Gly Glu Tyr Cys Lys Phe Pro Phe Leu Phe Asn
225                 230                 235                 240

Gly Lys Glu Tyr Asn Ser Cys Thr Asp Thr Gly Arg Ser Asp Gly Phe
                245                 250                 255

Leu Trp Cys Ser Thr Thr Tyr Asn Phe Glu Lys Asp Gly Lys Tyr Gly
            260                 265                 270

Phe Cys Pro His Glu Ala Leu Phe Thr Met Gly Gly Asn Ala Glu Gly
        275                 280                 285

Gln Pro Cys Lys Phe Pro Phe Arg Phe Gln Gly Thr Ser Tyr Asp Ser
    290                 295                 300

Cys Thr Thr Glu Gly Arg Thr Asp Gly Tyr Arg Trp Cys Gly Thr Thr
305                 310                 315                 320

Glu Asp Tyr Asp Arg Asp Lys Lys Tyr Gly Phe Cys Pro Glu Thr Ala
                325                 330                 335

Met Ser Thr Val Gly Gly Asn Ser Glu Gly Ala Pro Cys Val Phe Pro
            340                 345                 350

Phe Thr Phe Leu Gly Asn Lys Tyr Glu Ser Cys Thr Ser Ala Gly Arg
        355                 360                 365

Ser Asp Gly Lys Met Trp Cys Ala Thr Thr Ala Asn Tyr Asp Asp Asp
    370                 375                 380

Arg Lys Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val
385                 390                 395                 400

Ala Ala His Glu Phe Gly His Ala Met Gly Leu Glu His Ser Gln Asp
                405                 410                 415

Pro Gly Ala Leu Met Ala Pro Ile Tyr Thr Tyr Thr Lys Asn Phe Arg
            420                 425                 430

Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Glu Leu Tyr Gly Ala Ser
        435                 440                 445

Pro Asp Ile Asp Leu Gly Thr Gly Pro Thr Pro Thr Leu Gly Pro Val
    450                 455                 460
```

```
Thr Pro Glu Ile Cys Lys Gln Asp Ile Val Phe Asp Gly Ile Ala Gln
465                 470                 475                 480

Ile Arg Gly Glu Ile Phe Phe Phe Lys Asp Arg Phe Ile Trp Arg Thr
                485                 490                 495

Val Thr Pro Arg Asp Lys Pro Met Gly Pro Leu Leu Val Ala Thr Phe
            500                 505                 510

Trp Pro Glu Leu Pro Glu Lys Ile Asp Ala Val Tyr Glu Ala Pro Gln
        515                 520                 525

Glu Glu Lys Ala Val Phe Phe Ala Gly Asn Glu Tyr Trp Ile Tyr Ser
    530                 535                 540

Ala Ser Thr Leu Glu Arg Gly Tyr Pro Lys Pro Leu Thr Ser Leu Gly
545                 550                 555                 560

Leu Pro Pro Asp Val Gln Arg Val Asp Ala Ala Phe Asn Trp Ser Lys
                565                 570                 575

Asn Lys Lys Thr Tyr Ile Phe Ala Gly Asp Lys Phe Trp Arg Tyr Asn
            580                 585                 590

Glu Val Lys Lys Lys Met Asp Pro Gly Phe Pro Lys Leu Ile Ala Asp
        595                 600                 605

Ala Trp Asn Ala Ile Pro Asp Asn Leu Asp Ala Val Val Asp Leu Gln
    610                 615                 620

Gly Gly Gly His Ser Tyr Phe Phe Lys Gly Ala Tyr Tyr Leu Lys Leu
625                 630                 635                 640

Glu Asn Gln Ser Leu Lys Ser Val Lys Phe Gly Ser Ile Lys Ser Asp
                645                 650                 655

Trp Leu Gly Cys
            660

<210>  90
<211>  430
<212>  PRT
<213>  Homo Sapiens

<400>  90

Leu Arg Tyr Gln Gln Leu Ile Lys Glu Asn Leu Lys Glu Ile Ala Lys
1               5                   10                  15

Leu Ile Thr Leu Glu Gln Gly Lys Thr Leu Ala Asp Ala Glu Gly Asp
            20                  25                  30

Val Phe Arg Gly Leu Gln Val Val Glu His Ala Cys Ser Val Thr Ser
        35                  40                  45

Leu Met Met Gly Glu Thr Met Pro Ser Ile Thr Lys Asp Met Asp Leu
    50                  55                  60

Tyr Ser Tyr Arg Leu Pro Leu Gly Val Cys Ala Gly Ile Ala Pro Phe
```

65 70 75 80

Asn Phe Pro Ala Met Ile Pro Leu Trp Met Phe Pro Met Ala Met Val
85 90 95

Cys Gly Asn Thr Phe Leu Met Lys Pro Ser Glu Arg Val Pro Gly Ala
100 105 110

Thr Met Leu Leu Ala Lys Leu Leu Gln Asp Ser Gly Ala Pro Asp Gly
115 120 125

Thr Leu Asn Ile Ile His Gly Gln His Glu Ala Val Asn Phe Ile Cys
130 135 140

Asp His Pro Asp Ile Lys Ala Ile Ser Phe Val Gly Ser Asn Lys Ala
145 150 155 160

Gly Glu Tyr Ile Phe Glu Arg Gly Ser Arg His Gly Lys Arg Val Gln
165 170 175

Ala Asn Met Gly Ala Lys Asn His Gly Val Val Met Pro Asp Ala Asn
180 185 190

Lys Glu Asn Thr Leu Asn Gln Leu Val Gly Ala Ala Phe Gly Ala Ala
195 200 205

Gly Gln Arg Cys Met Ala Leu Ser Thr Ala Val Leu Val Gly Glu Ala
210 215 220

Lys Lys Trp Leu Pro Glu Leu Val Glu His Ala Lys Asn Leu Arg Val
225 230 235 240

Asn Ala Gly Asp Gln Pro Gly Ala Asp Leu Gly Pro Leu Ile Thr Pro
245 250 255

Gln Ala Lys Glu Arg Val Cys Asn Leu Ile Asp Ser Gly Thr Lys Glu
260 265 270

Gly Ala Ser Ile Leu Leu Asp Gly Arg Lys Ile Lys Val Lys Gly Tyr
275 280 285

Glu Asn Gly Asn Phe Val Gly Pro Thr Ile Ile Ser Asn Val Lys Pro
290 295 300

Asn Met Thr Cys Tyr Lys Glu Glu Ile Phe Gly Pro Val Leu Val Val
305 310 315 320

Leu Glu Thr Glu Thr Leu Asp Glu Ala Ile Gln Ile Val Asn Asn Asn
325 330 335

Pro Tyr Gly Asn Gly Thr Ala Ile Phe Thr Thr Asn Gly Ala Thr Ala
340 345 350

Arg Lys Tyr Ala His Leu Val Asp Val Gly Gln Val Gly Val Asn Val
355 360 365

Pro Ile Pro Val Pro Leu Pro Met Phe Ser Phe Thr Gly Ser Arg Ser
370 375 380

Ser Phe Arg Gly Asp Thr Asn Phe Tyr Gly Lys Gln Gly Ile Gln Phe

385 390 395 400

Tyr Thr Gln Leu Lys Thr Ile Thr Ser Gln Trp Lys Glu Glu Asp Ala
405 410 415

Thr Leu Ser Ser Pro Ala Val Val Met Pro Thr Met Gly Arg
420 425 430

<210> 91
<211> 1857
<212> PRT
<213> Homo Sapiens

<400> 91

Thr Tyr Ser Gly Leu Phe Cys Val Val Val Asn Pro Tyr Lys His Leu
1 5 10 15

Pro Ile Tyr Ser Glu Lys Ile Val Asp Met Tyr Lys Gly Lys Lys Arg
20 25 30

His Glu Met Pro Pro His Ile Tyr Ala Ile Ala Asp Thr Ala Tyr Arg
35 40 45

Ser Met Leu Gln Asp Arg Glu Asp Gln Ser Ile Leu Cys Thr Gly Glu
50 55 60

Ser Gly Ala Gly Lys Thr Glu Asn Thr Lys Lys Val Ile Gln Tyr Leu
65 70 75 80

Ala Val Val Ala Ser Ser His Lys Gly Lys Lys Asp Thr Ser Ile Thr
85 90 95

Gly Glu Leu Glu Lys Gln Leu Leu Gln Ala Asn Pro Ile Leu Glu Ala
100 105 110

Phe Gly Asn Ala Lys Thr Val Lys Asn Asp Asn Ser Ser Arg Phe Gly
115 120 125

Lys Phe Ile Arg Ile Asn Phe Asp Val Thr Gly Tyr Ile Val Gly Ala
130 135 140

Asn Ile Glu Thr Tyr Leu Leu Glu Lys Ser Arg Ala Ile Arg Gln Ala
145 150 155 160

Arg Asp Glu Arg Thr Phe His Ile Phe Tyr Tyr Met Ile Ala Gly Ala
165 170 175

Lys Glu Lys Met Arg Ser Asp Leu Leu Leu Glu Gly Phe Asn Asn Tyr
180 185 190

Thr Phe Leu Ser Asn Gly Phe Val Pro Ile Pro Ala Ala Gln Asp Asp
195 200 205

Glu Met Phe Gln Glu Thr Val Glu Ala Met Ala Ile Met Gly Phe Ser
210 215 220

Glu Glu Glu Gln Leu Ser Ile Leu Lys Val Val Ser Ser Val Leu Gln
225 230 235 240

```
Leu Gly Asn Ile Val Phe Lys Lys Glu Arg Asn Thr Asp Gln Ala Ser
                245                 250                 255

Met Pro Asp Asn Thr Ala Ala Gln Lys Val Cys His Leu Met Gly Ile
            260                 265                 270

Asn Val Thr Asp Phe Thr Arg Ser Ile Leu Thr Pro Arg Ile Lys Val
        275                 280                 285

Gly Arg Asp Val Val Gln Lys Ala Gln Thr Lys Glu Gln Ala Asp Phe
    290                 295                 300

Ala Val Glu Ala Leu Ala Lys Ala Thr Tyr Glu Arg Leu Phe Arg Trp
305                 310                 315                 320

Ile Leu Thr Arg Val Asn Lys Ala Leu Asp Lys Thr His Arg Gln Gly
                325                 330                 335

Ala Ser Phe Leu Gly Ile Leu Asp Ile Ala Gly Phe Glu Ile Phe Glu
            340                 345                 350

Val Asn Ser Phe Glu Gln Leu Cys Ile Asn Tyr Thr Asn Glu Lys Leu
        355                 360                 365

Gln Gln Leu Phe Asn His Thr Met Phe Ile Leu Glu Gln Glu Glu Tyr
    370                 375                 380

Gln Arg Glu Gly Ile Glu Trp Asn Phe Ile Asp Phe Gly Leu Asp Leu
385                 390                 395                 400

Gln Pro Cys Ile Glu Leu Ile Glu Arg Pro Asn Asn Pro Pro Gly Val
                405                 410                 415

Leu Ala Leu Leu Asp Glu Glu Cys Trp Phe Pro Lys Ala Thr Asp Lys
            420                 425                 430

Ser Phe Val Glu Lys Leu Cys Thr Glu Gln Gly Ser His Pro Lys Phe
        435                 440                 445

Gln Lys Pro Lys Gln Leu Lys Asp Lys Thr Glu Phe Ser Ile Ile His
    450                 455                 460

Tyr Ala Gly Lys Val Asp Tyr Asn Ala Ser Ala Trp Leu Thr Lys Asn
465                 470                 475                 480

Met Asp Pro Leu Asn Asp Asn Val Thr Ser Leu Leu Asn Ala Ser Ser
                485                 490                 495

Asp Lys Phe Val Ala Asp Leu Trp Lys Asp Val Asp Arg Ile Val Gly
            500                 505                 510

Leu Asp Gln Met Ala Lys Met Thr Glu Ser Ser Leu Pro Ser Ala Ser
        515                 520                 525

Lys Thr Lys Lys Gly Met Phe Arg Thr Val Gly Gln Leu Tyr Lys Glu
    530                 535                 540

Gln Leu Gly Lys Leu Met Thr Thr Leu Arg Asn Thr Thr Pro Asn Phe
545                 550                 555                 560
```

```
Val Arg Cys Ile Ile Pro Asn His Glu Lys Arg Ser Gly Lys Leu Asp
                565                 570                 575

Ala Phe Leu Val Leu Glu Gln Leu Arg Cys Asn Gly Val Leu Glu Gly
            580                 585                 590

Ile Arg Ile Cys Arg Gln Gly Phe Pro Asn Arg Ile Val Phe Gln Glu
        595                 600                 605

Phe Arg Gln Arg Tyr Glu Ile Leu Ala Ala Asn Ala Ile Pro Lys Gly
    610                 615                 620

Phe Met Asp Gly Lys Gln Ala Cys Ile Leu Met Ile Lys Ala Leu Glu
625                 630                 635                 640

Leu Asp Pro Asn Leu Tyr Arg Ile Gly Gln Ser Lys Ile Phe Phe Arg
                645                 650                 655

Thr Gly Val Leu Ala His Leu Glu Glu Glu Arg Asp Leu Lys Ile Thr
            660                 665                 670

Asp Val Ile Met Ala Phe Gln Ala Met Cys Arg Gly Tyr Leu Ala Arg
        675                 680                 685

Lys Ala Phe Ala Lys Arg Gln Gln Gln Leu Thr Ala Met Lys Val Ile
    690                 695                 700

Gln Arg Asn Cys Ala Ala Tyr Leu Lys Leu Arg Asn Trp Gln Trp Trp
705                 710                 715                 720

Arg Leu Phe Thr Lys Val Lys Pro Leu Leu Gln Val Thr Arg Gln Glu
                725                 730                 735

Glu Glu Met Gln Ala Lys Glu Asp Glu Leu Gln Lys Thr Lys Glu Arg
            740                 745                 750

Gln Gln Lys Ala Glu Asn Glu Leu Lys Glu Leu Glu Gln Lys His Ser
        755                 760                 765

Gln Leu Thr Glu Glu Lys Asn Leu Leu Gln Glu Gln Leu Gln Ala Glu
    770                 775                 780

Thr Glu Leu Tyr Ala Glu Ala Glu Glu Met Arg Val Arg Leu Ala Ala
785                 790                 795                 800

Lys Lys Gln Glu Leu Glu Glu Ile Leu His Glu Met Glu Ala Arg Leu
                805                 810                 815

Glu Glu Glu Glu Asp Arg Gly Gln Gln Leu Gln Ala Glu Arg Lys Lys
            820                 825                 830

Met Ala Gln Gln Met Leu Asp Leu Glu Glu Gln Leu Glu Glu Glu Glu
        835                 840                 845

Ala Ala Arg Gln Lys Leu Gln Leu Glu Lys Val Thr Ala Glu Ala Lys
    850                 855                 860

Ile Lys Lys Leu Glu Asp Glu Ile Leu Val Met Asp Asp Gln Asn Asn
865                 870                 875                 880
```

```
Lys Leu Ser Lys Glu Arg Lys Leu Leu Glu Glu Arg Ile Ser Asp Leu
                885                 890                 895

Thr Thr Asn Leu Ala Glu Glu Glu Glu Lys Ala Lys Asn Leu Thr Lys
            900                 905                 910

Leu Lys Asn Lys His Glu Ser Met Ile Ser Glu Leu Glu Val Arg Leu
        915                 920                 925

Lys Lys Glu Glu Lys Ser Arg Gln Glu Leu Glu Lys Leu Lys Arg Lys
    930                 935                 940

Leu Glu Gly Asp Ala Ser Asp Phe His Glu Gln Ile Ala Asp Leu Gln
945                 950                 955                 960

Ala Gln Ile Ala Glu Leu Lys Met Gln Leu Ala Lys Lys Glu Glu Glu
                965                 970                 975

Leu Gln Ala Ala Leu Ala Arg Leu Asp Asp Glu Ile Ala Gln Lys Asn
            980                 985                 990

Asn Ala Leu Lys Lys Ile Arg Glu  Leu Glu Gly His Ile  Ser Asp Leu
        995                 1000                1005

Gln Glu  Asp Leu Asp Ser Glu  Arg Ala Ala Arg Asn  Lys Ala Glu
    1010                1015                1020

Lys Gln  Lys Arg Asp Leu Gly  Glu Glu Leu Glu Ala  Leu Lys Thr
    1025                1030                1035

Glu Leu  Glu Asp Thr Leu Asp  Ser Thr Ala Thr Gln  Gln Glu Leu
    1040                1045                1050

Arg Ala  Lys Arg Glu Gln Glu  Val Thr Val Leu Lys  Lys Ala Leu
    1055                1060                1065

Asp Glu  Glu Thr Arg Ser His  Glu Ala Gln Val Gln  Glu Met Arg
    1070                1075                1080

Gln Lys  His Ala Gln Ala Val  Glu Glu Leu Thr Glu  Gln Leu Glu
    1085                1090                1095

Gln Phe  Lys Arg Ala Lys Ala  Asn Leu Asp Lys Asn  Lys Gln Thr
    1100                1105                1110

Leu Glu  Lys Glu Asn Ala Asp  Leu Ala Gly Glu Leu  Arg Val Leu
    1115                1120                1125

Gly Gln  Ala Lys Gln Glu Val  Glu His Lys Lys Lys  Lys Leu Glu
    1130                1135                1140

Ala Gln  Val Gln Glu Leu Gln  Ser Lys Cys Ser Asp  Gly Glu Arg
    1145                1150                1155

Ala Arg  Ala Glu Leu Asn Asp  Lys Val His Lys Leu  Gln Asn Glu
    1160                1165                1170

Val Glu  Ser Val Thr Gly Met  Leu Asn Glu Ala Glu  Gly Lys Ala
    1175                1180                1185
```

```
Ile Lys  Leu Ala Lys Asp Val  Ala Ser Leu Ser Ser  Gln Leu Gln
    1190                 1195                 1200

Asp Thr  Gln Glu Leu Leu Gln  Glu Glu Thr Arg Gln  Lys Leu Asn
    1205                 1210                 1215

Val Ser  Thr Lys Leu Arg Gln  Leu Glu Glu Glu Arg  Asn Ser Leu
    1220                 1225                 1230

Gln Asp  Gln Leu Asp Glu Glu  Met Glu Ala Lys Gln  Asn Leu Glu
    1235                 1240                 1245

Arg His  Ile Ser Thr Leu Asn  Ile Gln Leu Ser Asp  Ser Lys Lys
    1250                 1255                 1260

Lys Leu  Gln Asp Phe Ala Ser  Thr Val Glu Ala Leu  Glu Glu Gly
    1265                 1270                 1275

Lys Lys  Arg Phe Gln Lys Glu  Ile Glu Asn Leu Thr  Gln Gln Tyr
    1280                 1285                 1290

Glu Glu  Lys Ala Ala Ala Tyr  Asp Lys Leu Glu Lys  Thr Lys Asn
    1295                 1300                 1305

Arg Leu  Gln Gln Glu Leu Asp  Asp Leu Val Val Asp  Leu Asp Asn
    1310                 1315                 1320

Gln Arg  Gln Leu Val Ser Asn  Leu Glu Lys Lys Gln  Arg Lys Phe
    1325                 1330                 1335

Asp Gln  Leu Leu Ala Glu Glu  Lys Asn Ile Ser Ser  Lys Tyr Ala
    1340                 1345                 1350

Asp Glu  Arg Asp Arg Ala Glu  Ala Glu Ala Arg Glu  Lys Glu Thr
    1355                 1360                 1365

Lys Ala  Leu Ser Leu Ala Arg  Ala Leu Glu Glu Ala  Leu Glu Ala
    1370                 1375                 1380

Lys Glu  Glu Leu Glu Arg Thr  Asn Lys Met Leu Lys  Ala Glu Met
    1385                 1390                 1395

Glu Asp  Leu Val Ser Ser Lys  Asp Asp Val Gly Lys  Asn Val His
    1400                 1405                 1410

Glu Leu  Glu Lys Ser Lys Arg  Ala Leu Glu Thr Gln  Met Glu Glu
    1415                 1420                 1425

Met Lys  Thr Gln Leu Glu Glu  Leu Glu Asp Glu Leu  Gln Ala Thr
    1430                 1435                 1440

Glu Asp  Ala Lys Leu Arg Leu  Glu Val Asn Met Gln  Ala Leu Lys
    1445                 1450                 1455

Gly Gln  Phe Glu Arg Asp Leu  Gln Ala Arg Asp Glu  Gln Asn Glu
    1460                 1465                 1470

Glu Lys  Arg Arg Gln Leu Gln  Arg Gln Leu His Glu  Tyr Glu Thr
    1475                 1480                 1485
```

```
Glu Leu  Glu Asp Glu Arg Lys  Gln Arg Ala Leu Ala  Ala Ala Ala
     1490                 1495                 1500

Lys Lys  Lys Leu Glu Gly Asp  Leu Lys Asp Leu Glu  Leu Gln Ala
     1505                 1510                 1515

Asp Ser  Ala Ile Lys Gly Arg  Glu Glu Ala Ile Lys  Gln Leu Arg
     1520                 1525                 1530

Lys Leu  Gln Ala Gln Met Lys  Asp Phe Gln Arg Glu  Leu Glu Asp
     1535                 1540                 1545

Ala Arg  Ala Ser Arg Asp Glu  Ile Phe Ala Thr Ala  Lys Glu Asn
     1550                 1555                 1560

Glu Lys  Lys Ala Lys Ser Leu  Glu Ala Asp Leu Met  Gln Leu Gln
     1565                 1570                 1575

Glu Asp  Leu Ala Ala Ala Glu  Arg Ala Arg Lys Gln  Ala Asp Leu
     1580                 1585                 1590

Glu Lys  Glu Glu Leu Ala Glu  Glu Leu Ala Ser Ser  Leu Ser Gly
     1595                 1600                 1605

Arg Asn  Ala Leu Gln Asp Glu  Lys Arg Arg Leu Glu  Ala Arg Ile
     1610                 1615                 1620

Ala Gln  Leu Glu Glu Glu Leu  Glu Glu Glu Gln Gly  Asn Met Glu
     1625                 1630                 1635

Ala Met  Ser Asp Arg Val Arg  Lys Ala Thr Gln Gln  Ala Glu Gln
     1640                 1645                 1650

Leu Ser  Asn Glu Leu Ala Thr  Glu Arg Ser Thr Ala  Gln Lys Asn
     1655                 1660                 1665

Glu Ser  Ala Arg Gln Gln Leu  Glu Arg Gln Asn Lys  Glu Leu Arg
     1670                 1675                 1680

Ser Lys  Leu His Glu Met Glu  Gly Ala Val Lys Ser  Lys Phe Lys
     1685                 1690                 1695

Ser Thr  Ile Ala Ala Leu Glu  Ala Lys Ile Ala Gln  Leu Glu Glu
     1700                 1705                 1710

Gln Val  Glu Gln Glu Ala Arg  Glu Lys Gln Ala Ala  Thr Lys Ser
     1715                 1720                 1725

Leu Lys  Gln Lys Asp Lys Lys  Leu Lys Glu Ile Leu  Leu Gln Val
     1730                 1735                 1740

Glu Asp  Glu Arg Lys Met Ala  Glu Gln Tyr Lys Glu  Gln Ala Glu
     1745                 1750                 1755

Lys Gly  Asn Ala Arg Val Lys  Gln Leu Lys Arg Gln  Leu Glu Glu
     1760                 1765                 1770

Ala Glu  Glu Glu Ser Gln Arg  Ile Asn Ala Asn Arg  Arg Lys Leu
     1775                 1780                 1785
```

```
Gln Arg  Glu Leu Asp Glu Ala  Thr Glu Ser Asn Glu  Ala Met Gly
    1790                 1795                 1800

Arg Glu  Val Asn Ala Leu Lys  Ser Lys Leu Arg Arg  Gly Asn Glu
    1805                 1810                 1815

Thr Ser  Phe Val Pro Ser Arg  Arg Ser Gly Gly Arg  Arg Val Ile
    1820                 1825                 1830

Glu Asn  Ala Asp Gly Ser Glu  Glu Glu Thr Asp Thr  Arg Asp Ala
    1835                 1840                 1845

Asp Phe  Asn Gly Thr Lys Ala  Ser Glu
    1850                 1855
```

<210> 92
<211> 1953
<212> PRT
<213> Homo Sapiens

<400> 92

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Gly Cys Leu Cys Cys Ser Ser Glu Gln Leu Gln Glu Leu Pro Ser Arg
1               5                  10                  15

Glu Leu Gln Asp Ala Phe Pro Val Pro Leu Ala Gln Leu Pro Gln Gln
            20                  25                  30

Thr Thr Glu Lys Thr Val Thr Met Gly Asp Val Lys Leu Val Ala Ser
        35                  40                  45

Ser His Ile Ser Lys Thr Ser Leu Ser Val Asp Pro Ser Arg Val Asp
    50                  55                  60

Ser Met Pro Leu Thr Glu Ala Pro Ala Phe Ile Leu Pro Pro Arg Asn
65                  70                  75                  80

Leu Cys Ile Lys Glu Gly Ala Thr Ala Lys Phe Glu Gly Arg Val Arg
                85                  90                  95

Gly Tyr Pro Glu Pro Gln Val Thr Trp His Arg Asn Gly Gln Pro Ile
            100                 105                 110

Thr Ser Gly Gly Arg Phe Leu Leu Asp Cys Gly Ile Arg Gly Thr Phe
        115                 120                 125

Ser Leu Val Ile His Ala Val His Glu Glu Asp Arg Gly Lys Tyr Thr
    130                 135                 140

Cys Glu Ala Thr Asn Gly Ser Gly Ala Arg Gln Val Thr Val Glu Leu
145                 150                 155                 160

Thr Val Glu Gly Ser Phe Ala Lys Gln Leu Gly Gln Pro Val Val Ser
                165                 170                 175

Lys Thr Leu Gly Asp Arg Phe Ser Ala Ser Ala Val Glu Thr Arg Pro
            180                 185                 190

Ser Ile Trp Gly Glu Cys Pro Pro Lys Phe Ala Thr Lys Leu Gly Arg
        195                 200                 205
```

```
Val Val Val Lys Glu Gly Gln Met Gly Arg Phe Ser Cys Lys Ile Thr
    210                 215                 220

Gly Arg Pro Gln Pro Gln Val Thr Trp Leu Lys Gly Asn Val Pro Leu
225                 230                 235                 240

Gln Pro Ser Ala Arg Val Ser Val Ser Glu Lys Asn Gly Met Gln Val
                245                 250                 255

Leu Glu Ile His Gly Val Asn Gln Asp Asp Val Gly Val Tyr Thr Cys
            260                 265                 270

Leu Val Val Asn Gly Ser Gly Lys Ala Ser Met Ser Ala Glu Leu Ser
        275                 280                 285

Ile Gln Gly Leu Asp Ser Ala Asn Arg Ser Phe Val Arg Glu Thr Lys
    290                 295                 300

Ala Thr Asn Ser Asp Val Arg Lys Glu Val Thr Asn Val Ile Ser Lys
305                 310                 315                 320

Glu Ser Lys Leu Asp Ser Leu Glu Ala Ala Ala Lys Ser Lys Asn Cys
                325                 330                 335

Ser Ser Pro Gln Arg Gly Gly Ser Pro Pro Trp Ala Ala Asn Ser Gln
            340                 345                 350

Pro Gln Pro Pro Arg Glu Ser Lys Leu Glu Ser Cys Lys Asp Ser Pro
        355                 360                 365

Arg Thr Ala Pro Gln Thr Pro Val Leu Gln Lys Thr Ser Ser Ser Ile
    370                 375                 380

Thr Leu Gln Ala Ala Arg Val Gln Pro Glu Pro Arg Ala Pro Gly Leu
385                 390                 395                 400

Gly Val Leu Ser Pro Ser Gly Glu Glu Arg Lys Arg Pro Ala Pro Pro
                405                 410                 415

Arg Pro Ala Thr Phe Pro Thr Arg Gln Pro Gly Leu Gly Ser Gln Asp
            420                 425                 430

Val Val Ser Lys Ala Ala Asn Arg Arg Ile Pro Met Glu Gly Gln Arg
        435                 440                 445

Asp Ser Ala Phe Pro Lys Phe Glu Ser Lys Pro Gln Ser Gln Glu Val
    450                 455                 460

Lys Glu Asn Gln Thr Val Lys Phe Arg Cys Glu Val Ser Gly Ile Pro
465                 470                 475                 480

Lys Pro Glu Val Ala Trp Phe Leu Glu Gly Thr Pro Val Arg Arg Gln
                485                 490                 495

Glu Gly Ser Ile Glu Val Tyr Glu Asp Ala Gly Ser His Tyr Leu Cys
            500                 505                 510

Leu Leu Lys Ala Arg Thr Arg Asp Ser Gly Thr Tyr Ser Cys Thr Ala
        515                 520                 525
```

```
Ser Asn Ala Gln Gly Gln Val Ser Cys Ser Trp Thr Leu Gln Val Glu
    530                 535                 540

Arg Leu Ala Val Met Glu Val Ala Pro Ser Phe Ser Ser Val Leu Lys
545                 550                 555                 560

Asp Cys Ala Val Ile Glu Gly Gln Asp Phe Val Leu Gln Cys Ser Val
                565                 570                 575

Arg Gly Thr Pro Val Pro Arg Ile Thr Trp Leu Leu Asn Gly Gln Pro
            580                 585                 590

Ile Gln Tyr Ala Arg Ser Thr Cys Glu Ala Gly Val Ala Glu Leu His
        595                 600                 605

Ile Gln Asp Ala Leu Pro Glu Asp His Gly Thr Tyr Thr Cys Leu Ala
    610                 615                 620

Glu Asn Ala Leu Gly Gln Val Ser Cys Ser Ala Trp Val Thr Val His
625                 630                 635                 640

Glu Lys Lys Ser Ser Arg Lys Ser Glu Tyr Leu Leu Pro Val Ala Pro
                645                 650                 655

Ser Lys Pro Thr Ala Pro Ile Phe Leu Gln Gly Leu Ser Asp Leu Lys
            660                 665                 670

Val Met Asp Gly Ser Gln Val Thr Met Thr Val Gln Val Ser Gly Asn
        675                 680                 685

Pro Pro Pro Glu Val Ile Trp Leu His Asn Gly Asn Glu Ile Gln Glu
    690                 695                 700

Ser Glu Asp Phe His Phe Glu Gln Arg Gly Thr Gln His Ser Leu Trp
705                 710                 715                 720

Ile Gln Glu Val Phe Pro Glu Asp Thr Gly Thr Tyr Thr Cys Glu Ala
                725                 730                 735

Trp Asn Ser Ala Gly Glu Val Arg Thr Gln Ala Val Leu Thr Val Gln
            740                 745                 750

Glu Pro His Asp Gly Thr Gln Pro Trp Phe Ile Ser Lys Pro Arg Ser
        755                 760                 765

Val Thr Ala Ser Leu Gly Gln Ser Val Leu Ile Ser Cys Ala Ile Ala
    770                 775                 780

Gly Asp Pro Phe Pro Thr Val His Trp Leu Arg Asp Gly Lys Ala Leu
785                 790                 795                 800

Cys Lys Asp Thr Gly His Phe Glu Val Leu Gln Asn Glu Asp Val Phe
                805                 810                 815

Thr Leu Val Leu Lys Lys Val Gln Pro Trp His Ala Gly Gln Tyr Glu
            820                 825                 830

Ile Leu Leu Lys Asn Arg Val Gly Glu Cys Ser Cys Gln Val Ser Leu
        835                 840                 845
```

```
Met Leu Gln Asn Ser Ser Ala Arg Ala Leu Pro Arg Gly Arg Glu Pro
    850                 855                 860

Ala Ser Cys Glu Asp Leu Cys Gly Gly Gly Val Gly Ala Asp Gly Gly
865                 870                 875                 880

Gly Ser Asp Arg Tyr Gly Ser Leu Arg Pro Gly Trp Pro Ala Arg Gly
                885                 890                 895

Gln Gly Trp Leu Glu Glu Glu Asp Gly Glu Asp Val Arg Gly Val Leu
            900                 905                 910

Lys Arg Arg Val Glu Thr Arg Gln His Thr Glu Glu Ala Ile Arg Gln
        915                 920                 925

Gln Glu Val Glu Gln Leu Asp Phe Arg Asp Leu Leu Gly Lys Lys Val
    930                 935                 940

Ser Thr Lys Thr Leu Ser Glu Asp Asp Leu Lys Glu Ile Pro Ala Glu
945                 950                 955                 960

Gln Met Asp Phe Arg Ala Asn Leu Gln Arg Gln Val Lys Pro Lys Thr
                965                 970                 975

Val Ser Glu Glu Glu Arg Lys Val His Ser Pro Gln Gln Val Asp Phe
            980                 985                 990

Arg Ser Val Leu Ala Lys Lys Gly  Thr Ser Lys Thr Pro  Val Pro Glu
        995                 1000                1005

Lys Val  Pro Pro Pro Lys Pro  Ala Thr Pro Asp Phe  Arg Ser Val
    1010                1015                1020

Leu Gly  Gly Lys Lys Lys Leu  Pro Ala Glu Asn Gly  Ser Ser Ser
    1025                1030                1035

Ala Glu  Thr Leu Asn Ala Lys  Ala Val Glu Ser Ser  Lys Pro Leu
    1040                1045                1050

Ser Asn  Ala Gln Pro Ser Gly  Pro Leu Lys Pro Val  Gly Asn Ala
    1055                1060                1065

Lys Pro  Ala Glu Thr Leu Lys  Pro Met Gly Asn Ala  Lys Pro Ala
    1070                1075                1080

Glu Thr  Leu Lys Pro Met Gly  Asn Ala Lys Pro Asp  Glu Asn Leu
    1085                1090                1095

Lys Ser  Ala Ser Lys Glu Glu  Leu Lys Lys Asp Val  Lys Asn Asp
    1100                1105                1110

Val Asn  Cys Lys Arg Gly His  Ala Gly Thr Thr Asp  Asn Glu Lys
    1115                1120                1125

Arg Ser  Glu Ser Gln Gly Thr  Ala Pro Ala Phe Lys  Gln Lys Leu
    1130                1135                1140

Gln Asp  Val His Val Ala Glu  Gly Lys Lys Leu Leu  Leu Gln Cys
    1145                1150                1155
```

```
Gln Val  Ser Ser Asp Pro Pro  Ala Thr Ile Ile Trp  Thr Leu Asn
    1160                 1165                 1170

Gly Lys  Thr Leu Lys Thr Thr  Lys Phe Ile Ile Leu  Ser Gln Glu
    1175                 1180                 1185

Gly Ser  Leu Cys Ser Val Ser  Ile Glu Lys Ala Leu  Pro Glu Asp
    1190                 1195                 1200

Arg Gly  Leu Tyr Lys Cys Val  Ala Lys Asn Asp Ala  Gly Gln Ala
    1205                 1210                 1215

Glu Cys  Ser Cys Gln Val Thr  Val Asp Asp Ala Pro  Ala Ser Glu
    1220                 1225                 1230

Asn Thr  Lys Ala Pro Glu Met  Lys Ser Arg Arg Pro  Lys Ser Ser
    1235                 1240                 1245

Leu Pro  Pro Val Leu Gly Thr  Glu Ser Asp Ala Thr  Val Lys Lys
    1250                 1255                 1260

Lys Pro  Ala Pro Lys Thr Pro  Pro Lys Ala Ala Met  Pro Pro Gln
    1265                 1270                 1275

Ile Ile  Gln Phe Pro Glu Asp  Gln Lys Val Arg Ala  Gly Glu Ser
    1280                 1285                 1290

Val Glu  Leu Phe Gly Lys Val  Thr Gly Thr Gln Pro  Ile Thr Cys
    1295                 1300                 1305

Thr Trp  Met Lys Phe Arg Lys  Gln Ile Gln Glu Ser  Glu His Met
    1310                 1315                 1320

Lys Val  Glu Asn Ser Glu Asn  Gly Ser Lys Leu Thr  Ile Leu Ala
    1325                 1330                 1335

Ala Arg  Gln Glu His Cys Gly  Cys Tyr Thr Leu Leu  Val Glu Asn
    1340                 1345                 1350

Lys Leu  Gly Ser Arg Gln Ala  Gln Val Asn Leu Thr  Val Val Asp
    1355                 1360                 1365

Lys Pro  Asp Pro Pro Ala Gly  Thr Pro Cys Ala Ser  Asp Ile Arg
    1370                 1375                 1380

Ser Ser  Ser Leu Thr Leu Ser  Trp Tyr Gly Ser Ser  Tyr Asp Gly
    1385                 1390                 1395

Gly Ser  Ala Val Gln Ser Tyr  Ser Ile Glu Ile Trp  Asp Ser Ala
    1400                 1405                 1410

Asn Lys  Thr Trp Lys Glu Leu  Ala Thr Cys Arg Ser  Thr Ser Phe
    1415                 1420                 1425

Asn Val  Gln Asp Leu Leu Pro  Asp His Glu Tyr Lys  Phe Arg Val
    1430                 1435                 1440

Arg Ala  Ile Asn Val Tyr Gly  Thr Ser Glu Pro Ser  Gln Glu Ser
    1445                 1450                 1455
```

```
Glu Leu  Thr Thr Val Gly Glu  Lys Pro Glu Glu Pro  Lys Asp Glu
    1460                 1465                 1470

Val Glu  Val Ser Asp Asp Asp  Glu Lys Glu Pro Glu  Val Asp Tyr
    1475                 1480                 1485

Arg Thr  Val Thr Ile Asn Thr  Glu Gln Lys Val Ser  Asp Phe Tyr
    1490                 1495                 1500

Asp Ile  Glu Glu Arg Leu Gly  Ser Gly Lys Phe Gly  Gln Val Phe
    1505                 1510                 1515

Arg Leu  Val Glu Lys Lys Thr  Arg Lys Val Trp Ala  Gly Lys Phe
    1520                 1525                 1530

Phe Lys  Ala Tyr Ser Ala Lys  Glu Lys Glu Asn Ile  Arg Gln Glu
    1535                 1540                 1545

Ile Ser  Ile Met Asn Cys Leu  His His Pro Lys Leu  Val Gln Cys
    1550                 1555                 1560

Val Asp  Ala Phe Glu Glu Lys  Ala Asn Ile Val Met  Val Leu Glu
    1565                 1570                 1575

Ile Val  Ser Gly Gly Glu Leu  Phe Glu Arg Ile Ile  Asp Glu Asp
    1580                 1585                 1590

Phe Glu  Leu Thr Glu Arg Glu  Cys Ile Lys Tyr Met  Arg Gln Ile
    1595                 1600                 1605

Ser Glu  Gly Val Glu Tyr Ile  His Lys Gln Gly Ile  Val His Leu
    1610                 1615                 1620

Asp Leu  Lys Pro Glu Asn Ile  Met Cys Val Asn Lys  Thr Gly Thr
    1625                 1630                 1635

Arg Ile  Lys Leu Ile Asp Phe  Gly Leu Ala Arg Arg  Leu Glu Asn
    1640                 1645                 1650

Ala Gly  Ser Leu Lys Val Leu  Phe Gly Thr Pro Glu  Phe Val Ala
    1655                 1660                 1665

Pro Glu  Val Ile Asn Tyr Glu  Pro Ile Gly Tyr Ala  Thr Asp Met
    1670                 1675                 1680

Trp Ser  Ile Gly Val Ile Cys  Tyr Ile Leu Val Ser  Gly Leu Ser
    1685                 1690                 1695

Pro Phe  Met Gly Asp Asn Asp  Asn Glu Thr Leu Ala  Asn Val Thr
    1700                 1705                 1710

Ser Ala  Thr Trp Asp Phe Asp  Asp Glu Ala Phe Asp  Glu Ile Ser
    1715                 1720                 1725

Asp Asp  Ala Lys Asp Phe Ile  Ser Asn Leu Leu Lys  Lys Asp Met
    1730                 1735                 1740

Lys Asn  Arg Leu Asp Cys Thr  Gln Cys Leu Gln His  Pro Trp Leu
    1745                 1750                 1755
```

```
Met Lys  Asp Thr Lys Asn Met  Glu Ala Lys Lys Leu  Ser Lys Asp
    1760                  1765                  1770

Arg Met  Lys Lys Tyr Met Ala  Arg Arg Lys Trp Gln  Lys Thr Gly
    1775                  1780                  1785

Asn Ala  Val Arg Ala Ile Gly  Arg Leu Ser Ser Met  Ala Met Ile
    1790                  1795                  1800

Ser Gly  Leu Ser Gly Arg Lys  Ser Ser Thr Gly Ser  Pro Thr Ser
    1805                  1810                  1815

Pro Leu  Asn Ala Glu Lys Leu  Glu Ser Glu Glu Asp  Val Ser Gln
    1820                  1825                  1830

Ala Phe  Leu Glu Ala Val Ala  Glu Glu Lys Pro His  Val Lys Pro
    1835                  1840                  1845

Tyr Phe  Ser Lys Thr Ile Arg  Asp Leu Glu Val Val  Glu Gly Ser
    1850                  1855                  1860

Ala Ala  Arg Phe Asp Cys Lys  Ile Glu Gly Tyr Pro  Asp Pro Glu
    1865                  1870                  1875

Val Val  Trp Phe Lys Asp Asp  Gln Ser Ile Arg Glu  Ser Arg His
    1880                  1885                  1890

Phe Gln  Ile Asp Tyr Asp Glu  Asp Gly Asn Cys Ser  Leu Ile Ile
    1895                  1900                  1905

Ser Asp  Val Cys Gly Asp Asp  Asp Ala Lys Tyr Thr  Cys Lys Ala
    1910                  1915                  1920

Val Asn  Ser Leu Gly Glu Ala  Thr Cys Thr Ala Glu  Leu Ile Val
    1925                  1930                  1935

Glu Thr  Met Glu Glu Gly Glu  Gly Glu Gly Glu Glu  Glu Glu Glu
    1940                  1945                  1950
```

<210> 93
<211> 901
<212> PRT
<213> Homo Sapiens

<400> 93

```
Val Gly Arg Ala Arg Ala Pro Gly Ala Gln Val Gly Ala Gly Ala Met
1               5                  10                  15

Glu Pro Pro Thr Val Pro Ser Glu Arg Ser Leu Ser Leu Ser Leu Pro
            20                  25                  30

Gly Pro Arg Glu Gly Gln Ala Thr Leu Lys Pro Pro Pro Gln His Leu
        35                  40                  45

Trp Arg Gln Pro Arg Thr Pro Ile Arg Ile Gln Gln Arg Gly Tyr Ser
    50                  55                  60

Asp Ser Ala Glu Arg Ala Glu Arg Glu Arg Gln Pro His Arg Pro Ile
```

```
65                  70                  75                  80

Glu Arg Ala Asp Ala Met Asp Thr Ser Asp Arg Pro Gly Leu Arg Thr
                85                  90                  95

Thr Arg Met Ser Trp Pro Ser Ser Phe His Gly Thr Gly Thr Gly Ser
            100                 105                 110

Gly Gly Ala Gly Gly Gly Ser Ser Arg Arg Phe Glu Ala Glu Asn Gly
        115                 120                 125

Pro Thr Pro Ser Pro Gly Arg Ser Pro Leu Asp Ser Gln Ala Ser Pro
    130                 135                 140

Gly Leu Val Leu His Ala Gly Ala Ala Thr Ser Gln Arg Arg Glu Ser
145                 150                 155                 160

Phe Leu Tyr Arg Ser Asp Ser Asp Tyr Asp Met Ser Pro Lys Thr Met
                165                 170                 175

Ser Arg Asn Ser Ser Val Thr Ser Glu Ala His Ala Glu Asp Leu Ile
            180                 185                 190

Val Thr Pro Phe Ala Gln Val Leu Ala Ser Leu Arg Ser Val Arg Ser
        195                 200                 205

Asn Phe Ser Leu Leu Thr Asn Val Pro Val Pro Ser Asn Lys Arg Ser
    210                 215                 220

Pro Leu Gly Gly Pro Thr Pro Val Cys Lys Ala Thr Leu Ser Glu Glu
225                 230                 235                 240

Thr Cys Gln Gln Leu Ala Arg Glu Thr Leu Glu Glu Leu Asp Trp Cys
                245                 250                 255

Leu Glu Gln Leu Glu Thr Met Gln Thr Tyr Arg Ser Val Ser Glu Met
            260                 265                 270

Ala Ser His Lys Phe Lys Arg Met Leu Asn Arg Glu Leu Thr His Leu
        275                 280                 285

Ser Glu Met Ser Arg Ser Gly Asn Gln Val Ser Glu Tyr Ile Ser Thr
    290                 295                 300

Thr Phe Leu Asp Lys Gln Asn Glu Val Glu Ile Pro Ser Pro Thr Met
305                 310                 315                 320

Lys Glu Arg Glu Lys Gln Gln Ala Pro Arg Pro Arg Pro Ser Gln Pro
                325                 330                 335

Pro Pro Pro Pro Val Pro His Leu Gln Pro Met Ser Gln Ile Thr Gly
            340                 345                 350

Leu Lys Lys Leu Met His Ser Asn Ser Leu Asn Asn Ser Asn Ile Pro
        355                 360                 365

Arg Phe Gly Val Lys Thr Asp Gln Glu Glu Leu Leu Ala Gln Glu Leu
    370                 375                 380

Glu Asn Leu Asn Lys Trp Gly Leu Asn Ile Phe Cys Val Ser Asp Tyr
```

385 390 395 400

Ala Gly Gly Arg Ser Leu Thr Cys Ile Met Tyr Met Ile Phe Gln Glu
405 410 415

Arg Asp Leu Leu Lys Lys Phe Arg Ile Pro Val Asp Thr Met Val Thr
420 425 430

Tyr Met Leu Thr Leu Glu Asp His Tyr His Ala Asp Val Ala Tyr His
435 440 445

Asn Ser Leu His Ala Ala Asp Val Leu Gln Ser Thr His Val Leu Leu
450 455 460

Ala Thr Pro Ala Leu Asp Ala Val Phe Thr Asp Leu Glu Ile Leu Ala
465 470 475 480

Ala Leu Phe Ala Ala Ala Ile His Asp Val Asp His Pro Gly Val Ser
485 490 495

Asn Gln Phe Leu Ile Asn Thr Asn Ser Glu Leu Ala Leu Met Tyr Asn
500 505 510

Asp Glu Ser Val Leu Glu Asn His His Leu Ala Val Gly Phe Lys Leu
515 520 525

Leu Gln Glu Asp Asn Cys Asp Ile Phe Gln Asn Leu Ser Lys Arg Gln
530 535 540

Arg Gln Ser Leu Arg Lys Met Val Ile Asp Met Val Leu Ala Thr Asp
545 550 555 560

Met Ser Lys His Met Thr Leu Leu Ala Asp Leu Lys Thr Met Val Glu
565 570 575

Thr Lys Lys Val Thr Ser Ser Gly Val Leu Leu Leu Asp Asn Tyr Ser
580 585 590

Asp Arg Ile Gln Val Leu Arg Asn Met Val His Cys Ala Asp Leu Ser
595 600 605

Asn Pro Thr Lys Pro Leu Glu Leu Tyr Arg Gln Trp Thr Asp Arg Ile
610 615 620

Met Ala Glu Phe Phe Gln Gln Gly Asp Arg Glu Arg Glu Arg Gly Met
625 630 635 640

Glu Ile Ser Pro Met Cys Asp Lys His Thr Ala Ser Val Glu Lys Ser
645 650 655

Gln Val Gly Phe Ile Asp Tyr Ile Val His Pro Leu Trp Glu Thr Trp
660 665 670

Ala Asp Leu Val His Pro Asp Ala Gln Glu Ile Leu Asp Thr Leu Glu
675 680 685

Asp Asn Arg Asp Trp Tyr Tyr Ser Ala Ile Arg Gln Ser Pro Ser Pro
690 695 700

Pro Pro Glu Glu Glu Ser Arg Gly Pro Gly His Pro Pro Leu Pro Asp

705 710 715 720

Lys Phe Gln Phe Glu Leu Thr Leu Glu Glu Glu Glu Glu Glu Ile
725 730 735

Ser Met Ala Gln Ile Pro Cys Thr Ala Gln Glu Ala Leu Thr Ala Gln
740 745 750

Gly Leu Ser Gly Val Glu Glu Ala Leu Asp Ala Thr Ile Ala Trp Glu
755 760 765

Ala Ser Pro Ala Gln Glu Ser Leu Glu Val Met Ala Gln Glu Ala Ser
770 775 780

Leu Glu Ala Glu Leu Glu Ala Val Tyr Leu Thr Gln Gln Ala Gln Ser
785 790 795 800

Thr Gly Ser Ala Pro Val Ala Pro Asp Glu Phe Ser Ser Arg Glu Glu
805 810 815

Phe Val Val Ala Val Ser His Ser Ser Pro Ser Ala Leu Ala Leu Gln
820 825 830

Ser Pro Leu Leu Pro Ala Trp Arg Thr Leu Ser Val Ser Glu His Ala
835 840 845

Pro Gly Leu Pro Gly Leu Pro Ser Thr Ala Ala Glu Val Glu Ala Gln
850 855 860

Arg Glu His Gln Ala Ala Lys Arg Ala Cys Ser Ala Cys Ala Gly Thr
865 870 875 880

Phe Gly Glu Asp Thr Ser Ala Leu Pro Ala Pro Gly Gly Gly Gly Ser
885 890 895

Gly Gly Asp Pro Thr
900

<210> 94
<211> 702
<212> PRT
<213> Homo Sapiens

<400> 94

Pro Ala Ser Gly Arg Ala Pro Gln Pro Gly Arg Cys Thr Cys Gln Gly
1 5 10 15

Asn Lys Leu Glu Glu Gln Asp Pro Arg Pro Leu Gln Pro Ile Pro Gly
20 25 30

Leu Met Glu Gly Asn Lys Leu Glu Glu Gln Asp Ser Ser Pro Pro Gln
35 40 45

Ser Thr Pro Gly Leu Met Lys Gly Asn Lys Arg Glu Glu Gln Gly Leu
50 55 60

Gly Pro Glu Pro Ala Ala Pro Gln Gln Pro Thr Ala Glu Glu Glu Ala
65 70 75 80

```
Leu Ile Glu Phe His Arg Ser Tyr Arg Glu Leu Phe Glu Phe Phe Cys
                85                  90                  95

Asn Asn Thr Thr Ile His Gly Ala Ile Arg Leu Val Cys Ser Gln His
            100                 105                 110

Asn Arg Met Lys Thr Ala Phe Trp Ala Val Leu Trp Leu Cys Thr Phe
        115                 120                 125

Gly Met Met Tyr Trp Gln Phe Gly Leu Leu Phe Gly Glu Tyr Phe Ser
    130                 135                 140

Tyr Pro Val Ser Leu Asn Ile Asn Leu Asn Ser Asp Lys Leu Val Phe
145                 150                 155                 160

Pro Ala Val Thr Ile Cys Thr Leu Asn Pro Tyr Arg Tyr Pro Glu Ile
                165                 170                 175

Lys Glu Glu Leu Glu Glu Leu Asp Arg Ile Thr Glu Gln Thr Leu Phe
            180                 185                 190

Asp Leu Tyr Lys Tyr Ser Ser Phe Thr Thr Leu Val Ala Gly Ser Arg
        195                 200                 205

Ser Arg Arg Asp Leu Arg Gly Thr Leu Pro His Pro Leu Gln Arg Leu
    210                 215                 220

Arg Val Pro Pro Pro Pro His Gly Ala Arg Arg Ala Arg Ser Val Ala
225                 230                 235                 240

Ser Ser Leu Arg Asp Asn Asn Pro Gln Val Asp Trp Lys Asp Trp Lys
                245                 250                 255

Ile Gly Phe Gln Leu Cys Asn Gln Asn Lys Ser Asp Cys Phe Tyr Gln
            260                 265                 270

Thr Tyr Ser Ser Gly Val Asp Ala Val Arg Glu Trp Tyr Arg Phe His
        275                 280                 285

Tyr Ile Asn Ile Leu Ser Arg Leu Pro Glu Thr Leu Pro Ser Leu Glu
    290                 295                 300

Glu Asp Thr Leu Gly Asn Phe Ile Phe Ala Cys Arg Phe Asn Gln Val
305                 310                 315                 320

Ser Cys Asn Gln Ala Asn Tyr Ser His Phe His His Pro Met Tyr Gly
                325                 330                 335

Asn Cys Tyr Thr Phe Asn Asp Lys Asn Asn Ser Asn Leu Trp Met Ser
            340                 345                 350

Ser Met Pro Gly Ile Asn Asn Gly Leu Ser Leu Met Leu Arg Ala Glu
        355                 360                 365

Gln Asn Asp Phe Ile Pro Leu Leu Ser Thr Val Thr Gly Ala Arg Val
    370                 375                 380

Met Val His Gly Gln Asp Glu Pro Ala Phe Met Asp Asp Gly Gly Phe
385                 390                 395                 400
```

```
Asn Leu Arg Pro Gly Val Glu Thr Ser Ile Ser Met Arg Lys Glu Thr
                405                 410                 415

Leu Asp Arg Leu Gly Gly Asp Tyr Gly Asp Cys Thr Lys Asn Gly Ser
            420                 425                 430

Asp Val Pro Val Glu Asn Leu Tyr Pro Ser Lys Tyr Thr Gln Gln Val
        435                 440                 445

Cys Ile His Ser Cys Phe Gln Glu Ser Met Ile Lys Glu Cys Gly Cys
    450                 455                 460

Ala Tyr Ile Phe Tyr Pro Arg Pro Gln Asn Val Glu Tyr Cys Asp Tyr
465                 470                 475                 480

Arg Lys His Ser Ser Trp Gly Tyr Cys Tyr Tyr Lys Leu Gln Val Asp
                485                 490                 495

Phe Ser Ser Asp His Leu Gly Cys Phe Thr Lys Cys Arg Lys Pro Cys
            500                 505                 510

Ser Val Thr Ser Tyr Gln Leu Ser Ala Gly Tyr Ser Arg Trp Pro Ser
        515                 520                 525

Val Thr Ser Gln Glu Trp Val Phe Gln Met Leu Ser Arg Gln Asn Asn
    530                 535                 540

Tyr Thr Val Asn Asn Lys Arg Asn Gly Val Ala Lys Val Asn Ile Phe
545                 550                 555                 560

Phe Lys Glu Leu Asn Tyr Lys Thr Asn Ser Glu Ser Pro Ser Val Thr
                565                 570                 575

Met Val Thr Leu Leu Ser Asn Leu Gly Ser Gln Trp Ser Leu Trp Phe
            580                 585                 590

Gly Ser Ser Val Leu Ser Val Val Glu Met Ala Glu Leu Val Phe Asp
        595                 600                 605

Leu Leu Val Ile Met Phe Leu Met Leu Leu Arg Arg Phe Arg Ser Arg
    610                 615                 620

Tyr Trp Ser Pro Gly Arg Gly Gly Arg Gly Ala Gln Glu Val Ala Ser
625                 630                 635                 640

Thr Leu Ala Ser Ser Pro Pro Ser His Phe Cys Pro His Pro Met Ser
                645                 650                 655

Leu Ser Leu Ser Gln Pro Gly Pro Ala Pro Ser Pro Ala Leu Thr Ala
            660                 665                 670

Pro Pro Pro Ala Tyr Ala Thr Leu Gly Pro Arg Pro Ser Pro Gly Gly
        675                 680                 685

Ser Ala Gly Ala Ser Ser Ser Thr Cys Pro Leu Gly Gly Pro
    690                 695                 700
```

<210> 95
<211> 109
<212> PRT

<213> Homo Sapiens

<400> 95

```
Ala Tyr Ser Arg Gly Thr Ser Ser Leu Ser Thr Met Asn Gln Thr Ala
1               5                  10                  15

Ile Leu Ile Cys Cys Leu Ile Phe Leu Thr Leu Ser Gly Ile Gln Gly
            20                  25                  30

Val Pro Leu Ser Arg Thr Val Arg Cys Thr Cys Ile Ser Ile Ser Asn
        35                  40                  45

Gln Pro Val Asn Pro Arg Ser Leu Glu Lys Leu Glu Ile Ile Pro Ala
    50                  55                  60

Ser Gln Phe Cys Pro Arg Val Glu Ile Ile Ala Thr Met Lys Lys Lys
65                  70                  75                  80

Gly Glu Lys Arg Cys Leu Asn Pro Glu Ser Lys Ala Ile Lys Asn Leu
                85                  90                  95

Leu Lys Ala Val Ser Lys Glu Met Ser Lys Arg Ser Pro
            100                 105
```

<210> 96
<211> 249
<212> PRT
<213> Homo Sapiens

<400> 96

```
Glu Phe Pro Glu Glu Ala Asn Pro Ala Gly Ile Arg Ala Ile Arg Thr
1               5                  10                  15

Ala Thr Met Thr Val Gly Lys Ser Ser Lys Met Leu Gln His Ile Asp
            20                  25                  30

Tyr Arg Met Arg Cys Ile Leu Gln Asp Gly Arg Ile Phe Ile Gly Thr
        35                  40                  45

Phe Lys Ala Phe Asp Lys His Met Asn Leu Ile Leu Cys Asp Cys Asp
    50                  55                  60

Glu Phe Arg Lys Ile Lys Pro Lys Asn Ser Lys Gln Ala Glu Arg Glu
65                  70                  75                  80

Glu Lys Arg Val Leu Gly Leu Val Leu Leu Arg Gly Glu Asn Leu Val
                85                  90                  95

Ser Met Thr Val Glu Gly Pro Pro Pro Lys Asp Thr Gly Ile Ala Arg
            100                 105                 110

Val Pro Leu Ala Gly Ala Ala Gly Gly Pro Gly Ile Gly Arg Ala Ala
        115                 120                 125

Gly Arg Gly Ile Pro Ala Gly Val Pro Met Pro Gln Ala Pro Ala Gly
    130                 135                 140

Leu Ala Gly Pro Val Arg Gly Val Gly Gly Pro Ser Gln Gln Val Met
```

145 150 155 160

Thr Pro Gln Gly Arg Gly Thr Val Ala Ala Ala Ala Ala Ala Thr
165 170 175

Ala Ser Ile Ala Gly Ala Pro Thr Gln Tyr Pro Pro Gly Arg Gly Gly
180 185 190

Pro Pro Pro Pro Met Gly Arg Gly Ala Pro Pro Pro Gly Met Met Gly
195 200 205

Pro Pro Pro Gly Met Arg Pro Pro Met Gly Pro Pro Met Gly Ile Pro
210 215 220

Pro Gly Arg Gly Thr Pro Met Gly Met Pro Pro Pro Gly Met Arg Pro
225 230 235 240

Pro Pro Pro Gly Met Arg Gly Leu Leu
245

<210> 97
<211> 729
<212> PRT
<213> Homo Sapiens

<400> 97

Leu Leu Leu Trp Leu Asn Pro Gln Ala Leu Val Gly Ala Gln Gly Gly
1 5 10 15

Arg Met Ser Gln Trp Tyr Glu Leu Gln Gln Leu Asp Ser Lys Phe Leu
20 25 30

Glu Gln Val His Gln Leu Tyr Asp Asp Ser Phe Pro Met Glu Ile Arg
35 40 45

Gln Tyr Leu Ala Gln Trp Leu Glu Lys Gln Asp Trp Glu His Ala Ala
50 55 60

Asn Asp Val Ser Phe Ala Thr Ile Arg Phe His Asp Leu Leu Ser Gln
65 70 75 80

Leu Asp Asp Gln Tyr Ser Arg Phe Ser Leu Glu Asn Asn Phe Leu Leu
85 90 95

Gln His Asn Ile Arg Lys Ser Lys Arg Asn Leu Gln Asp Asn Phe Gln
100 105 110

Glu Asp Pro Ile Gln Met Ser Met Ile Ile Tyr Ser Cys Leu Lys Glu
115 120 125

Glu Arg Lys Ile Leu Glu Asn Ala Gln Arg Phe Asn Gln Ala Gln Ser
130 135 140

Gly Asn Ile Gln Ser Thr Val Met Leu Asp Lys Gln Lys Glu Leu Asp
145 150 155 160

Ser Lys Val Arg Asn Val Lys Asp Lys Val Met Cys Ile Glu His Glu
165 170 175

```
Ile Lys Ser Leu Glu Asp Leu Gln Asp Glu Tyr Asp Phe Lys Cys Lys
            180                 185                 190

Thr Leu Gln Asn Arg Glu His Glu Thr Asn Gly Val Ala Lys Ser Asp
        195                 200                 205

Gln Lys Gln Glu Gln Leu Leu Leu Lys Lys Met Tyr Leu Met Leu Asp
    210                 215                 220

Asn Lys Arg Lys Glu Val Val His Lys Ile Ile Glu Leu Leu Asn Val
225                 230                 235                 240

Thr Glu Leu Thr Gln Asn Ala Leu Ile Asn Asp Glu Leu Val Glu Trp
                245                 250                 255

Lys Arg Arg Gln Gln Ser Ala Cys Ile Gly Gly Pro Pro Asn Ala Cys
            260                 265                 270

Leu Asp Gln Leu Gln Asn Trp Phe Thr Ile Val Ala Glu Ser Leu Gln
        275                 280                 285

Gln Val Arg Gln Gln Leu Lys Lys Leu Glu Glu Leu Glu Gln Lys Tyr
    290                 295                 300

Thr Tyr Glu His Asp Pro Ile Thr Lys Asn Lys Gln Val Leu Trp Asp
305                 310                 315                 320

Arg Thr Phe Ser Leu Phe Gln Gln Leu Ile Gln Ser Ser Phe Val Val
                325                 330                 335

Glu Arg Gln Pro Cys Met Pro Thr His Pro Gln Arg Pro Leu Val Leu
            340                 345                 350

Lys Thr Gly Val Gln Phe Thr Val Lys Leu Arg Leu Leu Val Lys Leu
        355                 360                 365

Gln Glu Leu Asn Tyr Asn Leu Lys Val Lys Val Leu Phe Asp Lys Asp
    370                 375                 380

Val Asn Glu Arg Asn Thr Val Lys Gly Phe Arg Lys Phe Asn Ile Leu
385                 390                 395                 400

Gly Thr His Thr Lys Val Met Asn Met Glu Glu Ser Thr Asn Gly Ser
                405                 410                 415

Leu Ala Ala Glu Phe Arg His Leu Gln Leu Lys Glu Gln Lys Asn Ala
            420                 425                 430

Gly Thr Arg Thr Asn Glu Gly Pro Leu Ile Val Thr Glu Glu Leu His
        435                 440                 445

Ser Leu Ser Phe Glu Thr Gln Leu Cys Gln Pro Gly Leu Val Ile Asp
    450                 455                 460

Leu Glu Thr Thr Ser Leu Pro Val Val Val Ile Ser Asn Val Ser Gln
465                 470                 475                 480

Leu Pro Ser Gly Trp Ala Ser Ile Leu Trp Tyr Asn Met Leu Val Ala
                485                 490                 495
```

```
Glu Pro Arg Asn Leu Ser Phe Phe Leu Thr Pro Pro Cys Ala Arg Trp
            500                 505                 510

Ala Gln Leu Ser Glu Val Leu Ser Trp Gln Phe Ser Ser Val Thr Lys
        515                 520                 525

Arg Gly Leu Asn Val Asp Gln Leu Asn Met Leu Gly Glu Lys Leu Leu
    530                 535                 540

Gly Pro Asn Ala Ser Pro Asp Gly Leu Ile Pro Trp Thr Arg Phe Cys
545                 550                 555                 560

Lys Glu Asn Ile Asn Asp Lys Asn Phe Pro Phe Trp Leu Trp Ile Glu
                565                 570                 575

Ser Ile Leu Glu Leu Ile Lys Lys His Leu Leu Pro Leu Trp Asn Asp
            580                 585                 590

Gly Cys Ile Met Gly Phe Ile Ser Lys Glu Arg Glu Arg Ala Leu Leu
        595                 600                 605

Lys Asp Gln Gln Pro Gly Thr Phe Leu Leu Arg Phe Ser Glu Ser Ser
    610                 615                 620

Arg Glu Gly Ala Ile Thr Phe Thr Trp Val Glu Arg Ser Gln Asn Gly
625                 630                 635                 640

Gly Glu Pro Asp Phe His Ala Val Glu Pro Tyr Thr Lys Lys Glu Leu
                645                 650                 655

Ser Ala Val Thr Phe Pro Asp Ile Ile Arg Asn Tyr Lys Val Met Ala
            660                 665                 670

Ala Glu Asn Ile Pro Glu Asn Pro Leu Lys Tyr Leu Tyr Pro Asn Ile
        675                 680                 685

Asp Lys Asp His Ala Phe Gly Lys Tyr Tyr Ser Arg Pro Lys Glu Ala
    690                 695                 700

Pro Glu Pro Met Glu Leu Asp Gly Pro Lys Gly Thr Gly Tyr Ile Lys
705                 710                 715                 720

Thr Glu Leu Ile Ser Val Ser Glu Val
                725
```

<210> 98
<211> 1575
<212> PRT
<213> Homo Sapiens

<400> 98

```
Arg Gly Arg Leu Leu Gly Leu Leu Asn Pro Ser Val Ser Leu Gly Arg
1                   5                   10                  15

Pro Lys Val Arg Val Met Tyr Arg Asp Glu Cys Lys Lys His Leu Ala
            20                  25                  30

Gly Leu Gly Ala Leu Gly Leu Gly Ser Leu Ile Thr Glu Leu Thr Ala
        35                  40                  45
```

```
Asn Glu Glu Leu Thr Gly Thr Asp Gly Ala Leu Val Asn Asp Glu Gly
    50                  55                  60

Trp Val Arg Ser Thr Glu Asp Ala Val Asp Tyr Ser Asp Ile Asn Glu
65                  70                  75                  80

Val Ala Glu Asp Glu Ser Arg Arg Tyr Gln Gln Thr Met Gly Ser Leu
                85                  90                  95

Gln Pro Leu Cys His Ser Asp Tyr Asp Glu Asp Asp Tyr Asp Ala Asp
            100                 105                 110

Cys Glu Asp Ile Asp Cys Lys Leu Met Pro Pro Pro Pro Pro Pro Pro
        115                 120                 125

Gly Pro Met Lys Lys Asp Lys Asp Gln Asp Ser Ile Thr Gly Glu Lys
    130                 135                 140

Val Asp Phe Ser Ser Ser Ser Asp Ser Glu Ser Glu Met Gly Pro Gln
145                 150                 155                 160

Glu Ala Thr Gln Ala Glu Ser Glu Asp Gly Lys Leu Thr Leu Pro Leu
                165                 170                 175

Ala Gly Ile Met Gln His Asp Ala Thr Lys Leu Leu Pro Ser Val Thr
            180                 185                 190

Glu Leu Phe Pro Glu Phe Arg Pro Gly Lys Val Leu Arg Phe Leu Arg
        195                 200                 205

Leu Phe Gly Pro Gly Lys Asn Val Pro Ser Val Trp Arg Ser Ala Arg
    210                 215                 220

Arg Lys Arg Lys Lys Lys His Arg Glu Leu Ile Gln Glu Glu Gln Ile
225                 230                 235                 240

Gln Glu Val Glu Cys Ser Val Glu Ser Glu Val Ser Gln Lys Ser Leu
                245                 250                 255

Trp Asn Tyr Asp Tyr Ala Pro Pro Pro Pro Pro Glu Gln Cys Leu Ser
            260                 265                 270

Asp Asp Glu Ile Thr Met Met Ala Pro Val Glu Ser Lys Phe Ser Gln
        275                 280                 285

Ser Thr Gly Asp Ile Asp Lys Val Thr Asp Thr Lys Pro Arg Val Ala
    290                 295                 300

Glu Trp Arg Tyr Gly Pro Ala Arg Leu Trp Tyr Asp Met Leu Gly Val
305                 310                 315                 320

Pro Glu Asp Gly Ser Gly Phe Asp Tyr Gly Phe Lys Leu Arg Lys Thr
                325                 330                 335

Glu His Glu Pro Val Ile Lys Ser Arg Met Ile Glu Glu Phe Arg Lys
            340                 345                 350

Leu Glu Glu Asn Asn Gly Thr Asp Leu Leu Ala Asp Glu Asn Phe Leu
        355                 360                 365
```

```
Met Val Thr Gln Leu His Trp Glu Asp Asp Ile Ile Trp Asp Gly Glu
    370                 375                 380

Asp Val Lys His Lys Gly Thr Lys Pro Gln Arg Ala Ser Leu Ala Gly
385                 390                 395                 400

Trp Leu Pro Ser Ser Met Thr Arg Asn Ala Met Ala Tyr Asn Val Gln
                405                 410                 415

Gln Gly Phe Ala Ala Thr Leu Asp Asp Asp Lys Pro Trp Tyr Ser Ile
            420                 425                 430

Phe Pro Ile Asp Asn Glu Asp Leu Val Tyr Gly Arg Trp Glu Asp Asn
        435                 440                 445

Ile Ile Trp Asp Ala Gln Ala Met Pro Arg Leu Leu Glu Pro Pro Val
    450                 455                 460

Leu Thr Leu Asp Pro Asn Asp Glu Asn Leu Ile Leu Glu Ile Pro Asp
465                 470                 475                 480

Glu Lys Glu Glu Ala Thr Ser Asn Ser Pro Ser Lys Glu Ser Lys Lys
                485                 490                 495

Glu Ser Ser Leu Lys Lys Ser Arg Ile Leu Leu Gly Lys Thr Gly Val
            500                 505                 510

Ile Lys Glu Glu Pro Gln Gln Asn Met Ser Gln Pro Glu Val Lys Asp
        515                 520                 525

Pro Trp Asn Leu Ser Asn Asp Glu Tyr Tyr Tyr Pro Lys Gln Gln Gly
    530                 535                 540

Leu Arg Gly Thr Phe Gly Gly Asn Ile Ile Gln His Ser Ile Pro Ala
545                 550                 555                 560

Val Glu Leu Arg Gln Pro Phe Phe Pro Thr His Met Gly Pro Ile Lys
                565                 570                 575

Leu Arg Gln Phe His Arg Pro Pro Leu Lys Lys Tyr Ser Phe Gly Ala
            580                 585                 590

Leu Ser Gln Pro Gly Pro His Ser Val Gln Pro Leu Leu Lys His Ile
        595                 600                 605

Lys Lys Lys Ala Lys Met Arg Glu Gln Glu Arg Gln Ala Ser Gly Gly
    610                 615                 620

Gly Glu Met Phe Phe Met Arg Thr Pro Gln Asp Leu Thr Gly Lys Asp
625                 630                 635                 640

Gly Asp Leu Ile Leu Ala Glu Tyr Ser Glu Glu Asn Gly Pro Leu Met
                645                 650                 655

Met Gln Val Gly Met Ala Thr Lys Ile Lys Asn Tyr Tyr Lys Arg Lys
            660                 665                 670

Pro Gly Lys Asp Pro Gly Ala Pro Asp Cys Lys Tyr Gly Glu Thr Val
        675                 680                 685
```

```
Tyr Cys His Thr Ser Pro Phe Leu Gly Ser Leu His Pro Gly Gln Leu
    690                 695                 700

Leu Gln Ala Phe Glu Asn Asn Leu Phe Arg Ala Pro Ile Tyr Leu His
705                 710                 715                 720

Lys Met Pro Glu Thr Asp Phe Leu Ile Ile Arg Thr Arg Gln Gly Tyr
                725                 730                 735

Tyr Ile Arg Glu Leu Val Asp Ile Phe Val Val Gly Gln Gln Cys Pro
            740                 745                 750

Leu Phe Glu Val Pro Gly Pro Asn Ser Lys Arg Ala Asn Thr His Ile
        755                 760                 765

Arg Asp Phe Leu Gln Val Phe Ile Tyr Arg Leu Phe Trp Lys Ser Lys
    770                 775                 780

Asp Arg Pro Arg Arg Ile Arg Met Glu Asp Ile Lys Lys Ala Phe Pro
785                 790                 795                 800

Ser His Ser Glu Ser Ser Ile Arg Lys Arg Leu Lys Leu Cys Ala Asp
                805                 810                 815

Phe Lys Arg Thr Gly Met Asp Ser Asn Trp Trp Val Leu Lys Ser Asp
            820                 825                 830

Phe Arg Leu Pro Thr Glu Glu Glu Ile Arg Ala Met Val Ser Pro Glu
        835                 840                 845

Gln Cys Cys Ala Tyr Tyr Ser Met Ile Ala Ala Glu Gln Arg Leu Lys
    850                 855                 860

Asp Ala Gly Tyr Gly Glu Lys Ser Phe Phe Ala Pro Glu Glu Glu Asn
865                 870                 875                 880

Glu Glu Asp Phe Gln Met Lys Ile Asp Asp Glu Val Arg Thr Ala Pro
                885                 890                 895

Trp Asn Thr Thr Arg Ala Phe Ile Ala Ala Met Lys Gly Lys Cys Leu
            900                 905                 910

Leu Glu Val Thr Gly Val Ala Asp Pro Thr Gly Cys Gly Glu Gly Phe
        915                 920                 925

Ser Tyr Val Lys Ile Pro Asn Lys Pro Thr Gln Gln Lys Asp Asp Lys
    930                 935                 940

Glu Pro Gln Pro Val Lys Lys Thr Val Thr Gly Thr Asp Ala Asp Leu
945                 950                 955                 960

Arg Arg Leu Ser Leu Lys Asn Ala Lys Gln Leu Leu Arg Lys Phe Gly
                965                 970                 975

Val Pro Glu Glu Glu Ile Lys Lys Leu Ser Arg Trp Glu Val Ile Asp
            980                 985                 990

Val Val Arg Thr Met Ser Thr Glu  Gln Ala Arg Ser Gly  Glu Gly Pro
        995                 1000                1005
```

```
Met Ser  Lys Phe Ala Arg Gly  Ser Arg Phe Ser Val  Ala Glu His
    1010                 1015                 1020

Gln Glu  Arg Tyr Lys Glu Glu  Cys Gln Arg Ile Phe  Asp Leu Gln
    1025                 1030                 1035

Asn Lys  Val Leu Ser Ser Thr  Glu Val Leu Ser Thr  Asp Thr Asp
    1040                 1045                 1050

Ser Ser  Ser Ala Glu Asp Ser  Asp Phe Glu Glu Met  Gly Lys Asn
    1055                 1060                 1065

Ile Glu  Asn Met Leu Gln Asn  Lys Lys Thr Ser Ser  Gln Leu Ser
    1070                 1075                 1080

Arg Glu  Arg Glu Glu Gln Glu  Arg Lys Glu Leu Gln  Arg Met Leu
    1085                 1090                 1095

Leu Ala  Ala Gly Ser Ala Ala  Ser Gly Asn Asn His  Arg Asp Asp
    1100                 1105                 1110

Asp Thr  Ala Ser Val Thr Ser  Leu Asn Ser Ser Ala  Thr Gly Arg
    1115                 1120                 1125

Cys Leu  Lys Ile Tyr Arg Thr  Phe Arg Asp Glu Glu  Gly Lys Glu
    1130                 1135                 1140

Tyr Val  Arg Cys Glu Thr Val  Arg Lys Pro Ala Val  Ile Asp Ala
    1145                 1150                 1155

Tyr Val  Arg Ile Arg Thr Thr  Lys Asp Glu Glu Phe  Ile Arg Lys
    1160                 1165                 1170

Phe Ala  Leu Phe Asp Glu Gln  His Arg Glu Glu Met  Arg Lys Glu
    1175                 1180                 1185

Arg Arg  Arg Ile Gln Glu Gln  Leu Arg Arg Leu Lys  Arg Asn Gln
    1190                 1195                 1200

Glu Lys  Glu Lys Leu Lys Gly  Pro Pro Glu Lys Lys  Pro Lys Lys
    1205                 1210                 1215

Met Lys  Glu Arg Pro Asp Leu  Lys Leu Lys Cys Gly  Ala Cys Gly
    1220                 1225                 1230

Ala Ile  Gly His Met Arg Thr  Asn Lys Phe Cys Pro  Leu Tyr Tyr
    1235                 1240                 1245

Gln Thr  Asn Ala Pro Pro Ser  Asn Pro Val Ala Met  Thr Glu Glu
    1250                 1255                 1260

Gln Glu  Glu Glu Leu Glu Lys  Thr Val Ile His Asn  Asp Asn Glu
    1265                 1270                 1275

Glu Leu  Ile Lys Val Glu Gly  Thr Lys Ile Val Leu  Gly Lys Gln
    1280                 1285                 1290

Leu Ile  Glu Ser Ala Asp Glu  Val Arg Arg Lys Ser  Leu Val Leu
    1295                 1300                 1305
```

```
Lys Phe  Pro Lys Gln Gln Leu  Pro Pro Lys Lys Lys  Arg Arg Val
     1310                 1315                 1320

Gly Thr  Thr Val His Cys Asp  Tyr Leu Asn Arg Pro  His Lys Ser
     1325                 1330                 1335

Ile His  Arg Arg Arg Thr Asp  Pro Met Val Thr Leu  Ser Ser Ile
     1340                 1345                 1350

Leu Glu  Ser Ile Ile Asn Asp  Met Arg Asp Leu Pro  Asn Thr Tyr
     1355                 1360                 1365

Pro Phe  His Thr Pro Val Asn  Ala Lys Val Val Lys  Asp Tyr Tyr
     1370                 1375                 1380

Lys Ile  Ile Thr Arg Pro Met  Asp Leu Gln Thr Leu  Arg Glu Asn
     1385                 1390                 1395

Val Arg  Lys Arg Leu Tyr Pro  Ser Arg Glu Glu Phe  Arg Glu His
     1400                 1405                 1410

Leu Glu  Leu Ile Val Lys Asn  Ser Ala Thr Tyr Asn  Gly Pro Lys
     1415                 1420                 1425

His Ser  Leu Thr Gln Ile Ser  Gln Ser Met Leu Asp  Leu Cys Asp
     1430                 1435                 1440

Glu Lys  Leu Lys Glu Lys Glu  Asp Lys Leu Ala Arg  Leu Glu Lys
     1445                 1450                 1455

Ala Ile  Asn Pro Leu Leu Asp  Asp Asp Asp Gln Val  Ala Phe Ser
     1460                 1465                 1470

Phe Ile  Leu Asp Asn Ile Val  Thr Gln Lys Met Met  Ala Val Pro
     1475                 1480                 1485

Asp Ser  Trp Pro Phe His His  Pro Val Asn Lys Lys  Phe Val Pro
     1490                 1495                 1500

Asp Tyr  Tyr Lys Val Ile Val  Asn Pro Met Asp Leu  Glu Thr Ile
     1505                 1510                 1515

Arg Lys  Asn Ile Ser Lys His  Lys Tyr Gln Ser Arg  Glu Ser Phe
     1520                 1525                 1530

Leu Asp  Asp Val Asn Leu Ile  Leu Ala Asn Ser Val  Lys Tyr Asn
     1535                 1540                 1545

Asp Asn  Glu Cys Ser Ser Lys  Ala Asn Asp Ile Val  Cys Leu Ile
     1550                 1555                 1560

Gln Tyr  Cys Ser Ser Gln Ile  Glu Glu Leu Arg Phe
     1565                 1570                 1575
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<210> 99
<211> 166
<212> PRT
<213> Homo Sapiens

<400> 99

Leu Cys Leu Lys Lys Lys Ile Pro Asn Met Asp Lys Pro Arg Lys Glu
1 5 10 15

Asn Glu Glu Glu Pro Gln Ser Arg Pro Arg Pro Met Arg Arg Gly Leu
20 25 30

Arg Trp Ser Thr Leu Pro Lys Ser Ser Pro Pro Arg Ser Ser Leu Arg
35 40 45

Arg Ser Ser Pro Arg Arg Arg Ser Ser Phe Leu Arg Ser Ser Cys Leu
50 55 60

Ser Ser Cys Leu Arg Cys Ser Ser Arg Arg Thr Pro Ser Ala Gly Leu
65 70 75 80

Ser Arg Lys Asp Leu Phe Glu Val Arg Pro Pro Met Glu Gln Pro Pro
85 90 95

Cys Gly Val Gly Lys His Asn Leu Glu Glu Gly Ile Phe Lys Glu Arg
100 105 110

Leu Ala Arg Ser Arg Pro Gln Phe Arg Gly Asp Ile His Gly Arg Asn
115 120 125

Leu Ser Asn Glu Glu Met Ile Gln Ala Ala Asp Glu Leu Glu Glu Met
130 135 140

Lys Arg Val Arg Asn Lys Leu Met Ile Met His Trp Arg Ala Lys Arg
145 150 155 160

Gly Gly Pro Tyr Pro Ile
165

<210> 100
<211> 245
<212> PRT
<213> Homo Sapiens

<400> 100

Thr Lys Met Leu Lys Ser Trp Arg Ser Gly Arg Gln Ile Thr Gln Lys
1 5 10 15

Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu Lys Asp Ala
20 25 30

Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp Ala Glu Ala
35 40 45

Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu Glu Glu Leu
50 55 60

Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys Leu Glu Glu
65 70 75 80

Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys Val Ile Glu
85 90 95

```
Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln Glu Ile Gln
            100                 105                 110

Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg Lys Tyr Glu
        115                 120                 125

Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu Glu Arg Ala
    130                 135                 140

Glu Glu Arg Ala Glu Leu Ser Glu Gly Gln Val Arg Gln Leu Glu Glu
145                 150                 155                 160

Gln Leu Arg Ile Met Asp Gln Thr Leu Lys Ala Leu Met Ala Ala Glu
                165                 170                 175

Asp Lys Tyr Ser Gln Lys Glu Asp Arg Tyr Glu Glu Glu Ile Lys Val
            180                 185                 190

Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu Phe Ala Glu
        195                 200                 205

Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu Glu Glu Lys
    210                 215                 220

Val Leu Met Pro Lys Lys Lys Thr Leu Val Cys Ile Arg Cys Trp Ile
225                 230                 235                 240

Arg Leu Tyr Trp Ser
                245

<210>  101
<211>  267
<212>  PRT
<213>  Homo Sapiens

<400>  101

Leu Pro Val Leu Ala Ser Arg Ala Tyr Ala Ala Pro Ala Pro Gly Gln
1               5                   10                  15

Ala Leu Gln Arg Val Gly Ile Val Gly Gly Gln Glu Ala Pro Arg Ser
            20                  25                  30

Lys Trp Pro Trp Gln Val Ser Leu Arg Val Arg Asp Arg Tyr Trp Met
        35                  40                  45

His Phe Cys Gly Gly Ser Leu Ile His Pro Gln Trp Val Leu Thr Ala
    50                  55                  60

Ala His Cys Val Gly Pro Asp Val Lys Asp Leu Ala Ala Leu Arg Val
65                  70                  75                  80

Gln Leu Arg Glu Gln His Leu Tyr Tyr Gln Asp Gln Leu Leu Pro Val
                85                  90                  95

Ser Arg Ile Ile Val His Pro Gln Phe Tyr Thr Ala Gln Ile Gly Ala
            100                 105                 110

Asp Ile Ala Leu Leu Glu Leu Glu Glu Pro Val Lys Val Ser Ser His
        115                 120                 125
```

```
Val His Thr Val Thr Leu Pro Pro Ala Ser Glu Thr Phe Pro Pro Gly
    130                 135                 140

Met Pro Cys Trp Val Thr Gly Trp Gly Asp Val Asp Asn Asp Glu Arg
145                 150                 155                 160

Leu Pro Pro Pro Phe Pro Leu Lys Gln Val Lys Val Pro Ile Met Glu
                165                 170                 175

Asn His Ile Cys Asp Ala Lys Tyr His Leu Gly Ala Tyr Thr Gly Asp
            180                 185                 190

Asp Val Arg Ile Val Arg Asp Asp Met Leu Cys Ala Gly Asn Thr Arg
        195                 200                 205

Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Lys Val
    210                 215                 220

Asn Gly Thr Trp Leu Gln Ala Gly Val Val Ser Trp Gly Glu Gly Cys
225                 230                 235                 240

Ala Gln Pro Asn Arg Pro Gly Ile Tyr Thr Arg Val Thr Tyr Tyr Leu
                245                 250                 255

Asp Trp Ile His His Tyr Val Pro Lys Lys Pro
            260                 265
```

<210> 102
<211> 192
<212> PRT
<213> Homo Sapiens

<400> 102

```
Ala Arg Ala Ser Ser Cys Leu Ser Ala Asn Ala Ala Arg Met Ala Ser
1               5                   10                  15

Gln Asn Arg Asp Pro Ala Ala Thr Ser Val Ala Ala Ala Arg Lys Gly
            20                  25                  30

Ala Glu Pro Ser Gly Gly Ala Ala Arg Gly Pro Val Gly Lys Arg Leu
        35                  40                  45

Gln Gln Glu Leu Met Thr Leu Met Met Ser Gly Asp Lys Gly Ile Ser
    50                  55                  60

Ala Phe Pro Glu Ser Asp Asn Leu Phe Lys Trp Val Gly Thr Ile His
65                  70                  75                  80

Gly Ala Ala Gly Thr Val Tyr Glu Asp Leu Arg Tyr Lys Leu Ser Leu
                85                  90                  95

Glu Phe Pro Ser Gly Tyr Pro Tyr Asn Ala Pro Thr Val Lys Phe Leu
            100                 105                 110

Thr Pro Cys Tyr His Pro Asn Val Asp Thr Gln Gly Asn Ile Cys Leu
        115                 120                 125

Asp Ile Leu Lys Glu Lys Trp Ser Ala Leu Tyr Asp Val Arg Thr Ile
```

```
    130                 135                 140

Leu Leu Ser Ile Gln Ser Leu Leu Gly Glu Pro Asn Ile Asp Ser Pro
145                 150                 155                 160

Leu Asn Thr His Ala Ala Glu Leu Trp Lys Asn Pro Thr Ala Phe Lys
                165                 170                 175

Lys Tyr Leu Gln Glu Thr Tyr Ser Lys Gln Val Thr Ser Gln Glu Pro
            180                 185                 190
```